

# Mood & motivation in Parkinson's disease

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## **Mood & Motivation in Parkinson's disease**

Jennifer Reijnders

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# **Mood & Motivation in Parkinson's disease**

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**Promotor:**

Prof. dr. F.R.J. Verhey

**Copromotores:**

Dr. A.F.G. Leentjens

Dr. W.E.J. Weber

**Beoordelingscommissie:**

Prof. dr. H.W.M. Steinbusch (voorzitter)

Dr. P. Aalten

Prof. dr. P. van Harten

Prof. dr. R.C. van der Mast (Leids Universitair Medisch Centrum)

Dr. A. Winogrodzka (Medisch Centrum Alkmaar)

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# CHAPTER 1

## Psychopathology in Parkinson's disease: an introduction

### **Shaking palsy (Paralysis Agitans)**

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the sense and intellects being uninjured. Parkinson, 1817.



## MOOD & MOTIVATION IN PARKINSON'S DISEASE

## 1.1 Parkinson's disease

Parkinson's disease (PD) was first described in 1817 by the English physician named James Parkinson. He called it 'shaking palsy' with trembling and muscle weakness as the most important symptoms. His Essay on the Shaking Palsy was based on only six individuals <sup>1</sup>. Four decades later Jean-Martin Charcot added rigidity to Parkinson's clinical description and attached the name Parkinson's disease to the syndrome.

PD is the most common movement disorder and the second most common neurodegenerative disorder after Alzheimer's disease. The estimated prevalence of PD is 1-2% of the population over 65 years. This figure increases to 3-5% in people 85 years and older <sup>2</sup>. In the Netherlands, an overall incidence of 22.4 per 100.000 per year is reported. The incidence increases exponentially with age and is higher in men than in woman in all age groups, except in the 60 to 69 year old <sup>3</sup>.

A definite diagnosis of PD requires post-mortem confirmation. According to the Queens Square Brain Bank criteria, PD is defined by the presence of at least two of the four cardinal motor signs (resting tremor, rigidity, bradykinesia, and postural instability) and the absence of atypical features such as autonomic, pyramidal or cerebellar features or lack of response to dopaminergic treatment <sup>4</sup>.

The symptoms of PD are caused by a slow but progressive loss of neurons in the substantia nigra pars compacta accompanied by the presence of intraneuronal Lewy bodies. Braak and colleagues (2004) proposed a staging procedure of PD pathology. This staging procedure suggests a premotor period in which typical pathological changes, Lewy neuritis and Lewy bodies spread from the olfactory bulb and vagus nerve to lower brainstem regions (stages 1 to 2), followed by a symptomatic period when pathological changes involve the midbrain including substantia nigra (stage 3), mesocortex (stage 4), and eventually neocortex (stages 5 to 6) <sup>5</sup>. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging in vivo confirmed the loss not only of the brainstem dopaminergic system, in agreement with the severity of motor parkinsonism, but also of the serotonergic, noradrenergic, and cholinergic neurotransmitter systems, correlating with PD-related non-motor symptoms <sup>6, 7, 8</sup>.

## 1.2 Psychopathology in Parkinson's disease

In the past decade, it has become more and more recognized that in PD non-motor symptoms sometimes precede motor symptoms and that these symptoms significantly contribute to disability, reduced quality of life and caregiver distress <sup>9-13</sup>. Almost 90% of all PD patients experience non-motor symptoms during the course of the disease <sup>14</sup>. Non-motor symptoms may include mood disorders, cognitive deficits, hallucinations, olfactory disturbances, fatigue, pain, sleep disorders, and autonomic dysfunction.

This chapter focuses on the psychopathological symptoms in PD: depression, apathy, anxiety, cognitive impairment, and hallucinations. It presents an overview of studies conducted in this research area, focusing on epidemiology, diagnosis and assessment, and pathophysiology. At the end of this chapter the research questions for this thesis are formulated.

### Epidemiology

Prevalence rates of psychopathology in PD vary widely due to different assessment methods, selection of the population studied, type of disorder included and statistical method used. For *depressive syndromes* in PD, the prevalence rates vary between 2.7% and 90%. The lowest prevalence rates are reported in population studies, whereas studies in outpatient and inpatient settings tend to report higher prevalence rates<sup>10, 15, 16</sup>.

The prevalence of *apathy* in outpatient samples is reported to range from 16.5% to 51%<sup>17-19</sup>. In a community-based study of 232 PD patients, the prevalence of apathy was 38%. In 11% of the total sample apathy coexisted with depression and dementia, whereas 10% had apathy and depression, and 6.5% apathy and dementia<sup>20</sup>.

For *anxiety*, it is estimated that up to 40% of PD patients experience substantial anxiety. A recent international multi-centre study involving 342 PD patients reports a prevalence of an anxiety disorder defined by the criteria of the diagnostic and Statistical Manual (DSM IV)<sup>21</sup> of 34%. An additional 11.4% of the sample had clinically significant anxiety symptoms in the absence of a diagnosis of anxiety disorder<sup>22</sup>.

Cognitive impairment also occurs frequently in PD, it is estimated that *dementia* affects about 30% of PD patients<sup>23</sup>. Emre et al. (2003) showed that PD patients have a five-fold higher risk of developing dementia than their corresponding non-affected age group<sup>24</sup>. The cumulative prevalence is very high; at least 75% of PD patients who survive for more than 10 years will develop dementia<sup>25</sup>.

*Hallucinations* also belong to the most frequently observed psychopathological disturbances in PD, occurring in about 20-40% of patients receiving long term anti-parkinsonian medication<sup>26</sup>.

### Diagnosis and Assessment

Non-motor symptoms in PD are often underdiagnosed and undertreated<sup>27, 28</sup>. Diagnosing depression in PD can be difficult due to the considerable overlap of symptoms of depression and core symptoms of PD (e.g., psychomotor changes, attentional / concentration changes, loss of appetite / weight change, sleep disturbances, and fatigue). The most commonly used diagnostic classification for depression is the DSM IV<sup>21</sup>, although application of these criteria may miss a substantial number of patients with depression in PD. A workgroup from the National Institute for Neurological Diseases and Stroke

and the National Institute of Mental Health (NINDS/NIMH) recommended that an inclusive approach should be used by diagnosing depression in PD. This means all symptoms should be considered as related to depression, regardless of their overlap with PD or other medical conditions<sup>29</sup>.

Symptoms of apathy and depression are closely related and sometimes difficult to recognize or distinguish from each other in PD patients. The concept of apathy as a syndrome in itself and not as a symptom of depression, has gained more attention. Only recently, diagnostic criteria have been proposed for apathy<sup>30</sup>. Mulin et al. (2010) validated these criteria in a population of different neuropsychiatric diseases<sup>31</sup>.

Anxiety is most commonly diagnosed by the diagnostic criteria of the DSM IV<sup>21</sup>. A differentiation between non-episodic (generalized anxiety disorder, agoraphobia, social phobia) and episodic (panic disorder) anxiety disorder can be made. The comorbidity of anxiety and depression in PD is high and the application of the DSM anxiety criteria in PD has the same difficulties of symptomatic overlap. Also short-lasting anxiety episodes related to motor fluctuations do not fulfill criteria for any specific DSM IV anxiety disorder<sup>32</sup>.

In 2007, a Task Force of the Movement Disorder Society (MDS) defined clinical diagnostic criteria for probable and possible PD-dementia (PDD) and practical guidelines to establish the diagnosis and characterize the disorder. Core features, which must be met, include the diagnosis of PD according to Queen Square Brain Bank criteria, PD developed prior to the onset of dementia, mini mental state exam score below 26, cognitive deficits in more than one cognitive domain and severe enough to impact daily living<sup>33, 34</sup>.

Recently, the NIMH proposed criteria for PD-associated psychosis, including hallucinations. The criteria are inclusive and contain descriptions of the full range of characteristic symptoms, chronology of onset, duration of symptoms, exclusionary diagnosis and associated features such as dementia<sup>35</sup>.

Although a diagnosis should be made using clinical criteria, rating scales are often used for screening or assessment of severity of psychopathological symptoms in PD. MDS task forces have reviewed rating scales for depression, apathy, anxiety, and hallucinations in PD and reported evaluations and recommendations. The most appropriate scale is dependent on the clinical or research goal<sup>32, 36-38</sup>.

### **Pathophysiology**

Studies addressing the pathophysiology of psychopathological symptoms in PD have shifted attention from the dopaminergic neurotransmitter system to other neurotransmitter systems. The pathophysiology of depression, apathy, anxiety, PDD, and hallucinations probably includes dopaminergic, serotonergic, noradrenergic, and cholinergic mechanisms<sup>39, 40</sup>.

## **1.3 Aims of this thesis**

### **Identifying patient subgroups**

There is substantial variability among PD patients: variability in the progression of the disease as well as variability in the clinical expression of motor and non-motor symptoms. Previous studies addressing different subtypes of PD patients focused mainly on the motor symptoms. Separation into tremor-dominant subtype, hypokinetic-rigid subtype, and postural instability / gait difficulty subtype has been the most extensively studied<sup>41-43</sup>. Identification of different subtypes of PD patients based on motor and psychopathological symptoms can lead to important insights.

### **Diagnostic issues**

Psychopathological symptoms of PD have gained more and more attention during the last decade. This has led to a number of diagnostic problems and questions. This thesis focuses on diagnostic issues of two very common neuropsychiatric symptoms in patients with PD: depression and apathy.

Although it is known that depression and apathy are very common in PD patients, the variability in reported prevalence rates is enormous and comparison between studies is difficult due to differences in samples included and diagnostic methods used. A major problem in diagnosing depression in PD is the considerable overlap in symptoms of depression and symptoms of PD. An 'inclusive' approach has been adopted by which present symptoms constitute to the diagnosis of depression, even though these symptoms could also be attributed to PD. Rating scales for depression in PD, which are used to screen or assess the severity of depression, often incorporate varying numbers of depressive and somatic symptoms.

Another diagnostic issue comprises the overlap between depression and apathy. On the one hand, depressive patients often have apathetic symptoms; apathy may therefore be one of the clinical signs of depression. On the other hand, apathy can also be seen as a core feature of PD and recent studies have support the notion that apathy can be discerned from depression<sup>18, 44, 45</sup>. Recently, diagnostic criteria for apathy in

neuropsychiatric disorders have been proposed, but these criteria need thorough validation in PD patients. Besides this, there is currently little knowledge about the pathophysiology of apathy in PD.

The main research questions of this thesis are:

- Can we establish subtypes of PD patients on the basis of motor and psychopathological symptoms?
- What is the prevalence of depression and apathy in PD patients?
- How do motor symptoms contribute to the diagnosis of depression in PD?
- Are the proposed diagnostic criteria for apathy valid?
- What are the neuroanatomical correlates of apathy in PD patients?

## 1.4 Outline of this thesis

Chapter 2 provides a systematic review of prevalence studies of depression in PD. In the literature, reported prevalence rates of depressive syndromes in PD vary widely. Possible reasons for this variation include the nature of the population studied, the way the diagnosis is established, the types of depressive disorder included and the statistical measures used. We carried out a systematic literature search and quality assessment criteria were used to ensure a minimum quality of studies included in the review.

Chapter 3 is concerned with the influence of somatic symptoms in depression rating scales on the diagnosis and assessment of depression in PD. The recognition and assessment of depression in PD patients is often difficult due to overlap between PD and depressive symptoms. Currently an inclusive approach is adopted, which incorporates that adjusted cut-off scores need to be used for PD patients. Another approach could be to adjust the depression rating scales, excluding the somatic items. We investigated the influence of somatic symptoms on the clinimetric performance of two commonly used depression rating scales; the Hamilton Depression Rating Scale and Montgomery-Åsberg Depression Rating Scale.

Chapter 4 describes a cluster analysis performed with motor and psychopathological symptoms that aims at identifying subtypes of PD not only on the basis of motor symptoms, but on the basis of psychopathological and motor symptoms. Different subtypes of motor symptoms in PD have been described and it has been suggested that the various motor presentations of PD are also characterized by a different risk and severity of specific neuropsychiatric symptoms. The question is can we establish

homogeneous subtypes of PD patients on the basis of both motor and psychopathological symptoms.

Chapter 5 describes a validation study of proposed diagnostic criteria of apathy in a population of PD patients. Research and clinical practice have been hampered by a lack of generally accepted diagnostic criteria. A consensus meeting of experts has recently led to proposed diagnostic criteria. Our purpose was to validate these proposed diagnostic criteria for apathy in a PD population.

Chapter 6 investigates the structural correlates of apathy in the brains of PD patients. There are only few studies addressing the neuroanatomical correlate of apathy in PD. Involvement of the prefrontal-basal ganglia system has been hypothesized. We investigated the structural correlates by correlating the level of apathy with anatomical changes in grey matter density, derived from magnetic resonance imaging scans.

Chapter 7 summarizes and discusses the main findings of this thesis. Clinical implications and directions for further research are given.

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## MOOD & MOTIVATION IN PARKINSON'S DISEASE

The background of the page is a grayscale abstract image. It features several bright, diagonal light rays or streaks that intersect across the frame. In the lower-left quadrant, there is a large, bright, out-of-focus shape that resembles a stylized flower or a cluster of petals, with a very bright white center. The overall effect is ethereal and artistic.

## CHAPTER 2

### A systematic review of prevalence studies of depression in Parkinson's disease

*Reijnders JSAM, Ehrt U, Weber WEJ, Aarsland D, Leentjens AFG.  
Movement Disorders 2008;23:183-189.*

## **Abstract**

Prevalence rates of depressive disorders in Parkinson's disease (PD) vary widely across studies, ranging from 2.7% to more than 90%. The aim of this systematic review was to calculate average prevalences of depressive disorders taking into account the different settings and different diagnostic approaches of studies. Using Medline on Pubmed, a systematic literature search was carried out for studies of depression in Parkinson's disease. A total of 104 articles were included and assessed for quality; 51 articles fulfilled the quality criteria. Multiple publications from the same database were not included in the meta-analysis. In the remaining 36 articles, the weighted prevalence of major depressive disorder was 17% of PD patients, that of minor depression 22% and dysthymia 13%. Clinically significant depressive symptoms, irrespective of the presence of a DSM defined depressive disorder, were present in 35%. In studies using a (semi-) structured interview to establish DSM criteria, the reported prevalence of major depressive disorder was 19%, while in studies using DSM criteria without a structured interview, the reported prevalence of major depressive disorder was 7%. Population studies report lower prevalence rates for both major depressive disorder and the clinically significant depressive symptoms than studies in other settings. This systematic review suggests that the average prevalence of major depressive disorder in PD is substantial, but lower than generally assumed.

## 2.1 Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by tremor, bradykinesia, rigidity, and postural instability. In addition, a high prevalence of psychopathologic syndromes is reported, including affective disorders, cognitive deterioration, and perceptual and behavioural symptoms. Depression is known to have a major impact on the prognosis of PD: depressed PD patients score lower on scales assessing motor function and activities of daily living (ADL), exhibit more cognitive symptoms, and report a lower quality of life <sup>1-3</sup>. Despite this, depression in PD is underdiagnosed and undertreated <sup>4,5</sup>.

Prevalence rates of depressive syndromes in PD that are reported in the literature vary widely, ranging from 2.7% to more than 90% <sup>6-8</sup>. Possible reasons for this variation include the nature of the population studied, the way the diagnosis is established, the types of depressive disorder included in the study, and the statistical measures used. In studies assessing the presence of depressive disorders in patients with physical comorbidity in general, the lowest prevalences are reported in population studies, whereas studies in outpatient and inpatient settings tend to report higher prevalence rates. Studies measuring depressive symptoms on a rating scale may yield higher prevalences than studies using diagnostic criteria for depression, such as those of the Diagnostic and Statistical Manual for mental disorders (DSM) of the American Psychiatric Association (APA) or the International Classification of Diseases (ICD) of the World Health Organisation (WHO) <sup>9, 10</sup>. Studies using a structured or semi-structured interview probably yield the most conservative estimates <sup>11</sup>. Even if diagnostic criteria are used, the approach to these criteria may influence prevalence rates: an 'inclusive' approach yields a higher prevalence than an 'exclusive' approach <sup>12</sup>. When rating scales are used, self-report instruments tend to give higher prevalences than observer rated instruments. Prevalences are influenced by the syndromes included in the study: major depressive disorder only, or less severe syndromes such as dysthymia and minor depression. Finally: some studies use point-prevalences, whereas others use monthly prevalences, which may give rise to different prevalence rates.

All these factors make it difficult to estimate the extent to which depression complicates PD. The aim of this systematic review is to calculate average prevalences of depressive disorders taking the different settings and the different approaches to diagnosis of studies into account.

## 2.2 Methods

### Search strategy

A systematic literature search was carried out in Medline using Pubmed. The entire time scale was used up to February 2007 (included). The following keywords were used to carry out multiple searches: 'Parkinson', 'depression', 'prevalence', and 'incidence'. In total 272 articles were retrieved. The abstracts of these 272 articles were read. All articles with potential reference to the prevalence of depression were included (122). If no abstract was available, the article was nevertheless included. Further articles were identified from the reference lists of the selected articles as well as from previous review studies. Articles in languages other than English, German, French, and Dutch, were excluded (5). A total of 165 articles were read in full. After reading these articles, another 61 articles were excluded because of the following reasons: there was no reference to the prevalence of depression (49), patients with depression were excluded (5), the population did not include PD patients (2), depression was only related to 'off'-periods (1), and case reports or reviews (4). The remaining 104 articles were included and underwent quality assessment.

### Quality assessment

The included articles were read in full and quality rated by three of the authors (JR, UE, DA). For 3 studies an unclarity in one of the domains was checked with the first author of the study. In case of discrepancies between the raters, consensus was achieved after discussion. If consensus was not reached, articles were re-assessed by the last author (AL) who made a final decision. The quality assessment used criteria adapted from Aarsland et al. as shown in Table 1<sup>13</sup>. In order to ensure a minimum quality of studies included in the review, only studies that scored at least one point on all three criteria: case identification, diagnostic criteria for PD, and diagnostic criteria for depression, were included. The full list of assessed studies is given in Reijnders, Ehrt, et al. (2008).

**Table 1.** Quality assessment criteria as adapted from Aarsland et al. (2005)<sup>13</sup>  
Studies are scored from 0 to 3 in three different domains, yielding a maximum score of 9

Score	Case Identification	Diagnostic criteria for PD	Diagnostic Criteria for depression
3	Door-to-door survey, or questionnaire survey of total/random sample	Clinical diagnosis using accepted criteria and autopsy verification	Use of a (semi-) structured interview to establish a diagnosis based on standardized and widely used criteria (DSM, ICD or RDC) <sup>16</sup>
2	Multiple sources used to identify cases (GP registration, nursing homes registration, private specialists records, hospital records, patient support groups, drug prescriptions database, etc)	Established and accepted diagnostic criteria such as United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria	Standardized and widely used criteria (DSM, ICD or RDC) without a (semi-) structured clinical interview
1	Single source of patients (GP registration, hospital files, or convenience sample of outpatients)	Limited description of clinical inclusion and exclusion criteria	Cut-off score on a depression rating scale
0	No information	No or very limited information	No or inadequate criteria (e.g., subjective clinical impression)

### Selection of studies

During the assessment phase it became clear that several publications stemmed from the same databases. Inclusion of multiple publications from the same study population, would lead to a disproportional influence of these studies on the calculated prevalence rates. The authors therefore contacted the first author of those studies to check whether they were indeed based on the same sample. In all but one case the authors received an answer. They decided to follow the following strategy: if studies were based on the same sample, only the first publication was included in the meta-analysis. If for some reason, studies based on the same sample had varying numbers of patients included, the study with the highest number of patients was included. For studies based on cumulative databases, only the most recent publication with the highest number of patients was included. Some publications were based on joint databases from within a single or between several research groups and in this case only the publication stemming from the combined database was included in the meta-analysis. The set of studies that we received no information on were presumed to come from the same database.



### Statistics

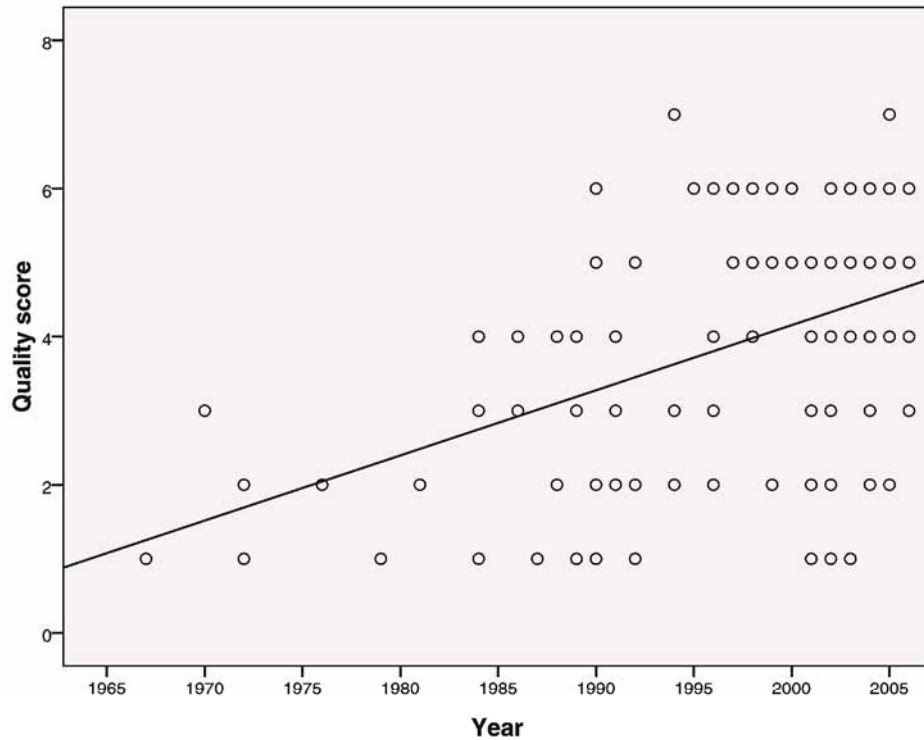
Data are presented as numbers and proportions. Descriptive data are presented as mean with 95% confidence intervals (95% CI). For studies that assessed specific depressive disorders, the prevalences were recorded. In addition, the percentage of patients with 'clinically relevant depressive symptoms' was scored. For studies that assessed both one or more depressive disorders either separately, or combined, this percentage equals the combined prevalences of all depressive disorders. For studies using cut-off scores on rating scales, where no DSM diagnoses are available, this percentage represents the presence of depressive symptoms in a clinically relevant severity, as reflected by the number of patients scoring above the set cut-off was taken as the 'overall prevalence of depression'.

Prevalence rates across studies were calculated as weighted means. The prevalence rate per study was multiplied by the corresponding sample size and divided by the total sample size of all studies. Comparison of proportions was done with Chi-square tests. SPSS version 12.0 (SPSS, Chicago) was used for statistical calculations.

## 2.3 Results

Of a total of 104 studies, 22 studies focused on the prevalence of depression in PD as a primary study objective; the remaining 82 studies had other primary objectives but also reported on the prevalence of depression in the study sample. There were 16 population-based studies, 3 studies in general practices, 71 studies in outpatient settings, 5 studies in hospital inpatient settings, and 2 studies in nursing homes. Another 7 studies used patients from a combination of different settings: population and outpatient samples (4), outpatient and inpatient samples (2), and outpatient and nursing home samples (1). In some of the studies in outpatient settings, the population was restricted to a specific subgroup: patients screened for possible DBS-screening (3), patients on long-term levodopa treatment (3), de novo patients (3), and patients with concurrent dementia (1). Different diagnostic criteria for depression were used: 31 studies used a (semi-) structured interview to establish DSM criteria, 20 studies used DSM criteria without a (semi-) structured interview, 38 studies used a cut-off score on a depression rating scale, and 15 studies used no or inadequate criteria to diagnose depression.

Quality was assessed of all 104 studies according to the criteria shown in Table 1. The maximum score for quality according to these criteria is 9. The actual scores ranged from 1 to 7, with a mean of 3.77 (SD: 1.73). The quality of depression studies in PD increases over time as shown in Figure 1. Of the 104 studies, 51 fulfilled the quality criteria. After excluding studies based on the same, cumulative or joint databases, 36 studies were included in the review.



**Figure 1.** Increment of the quality score over time  
Scatterplot of quality scores of the included studies from 1965 onwards, showing an increase in quality over time. The regression line indicates average quality scores over time

The prevalences of major depressive disorder, minor depression, and dysthymia, as well as clinically significant depressive symptoms are shown in Tables 2A, 2B, and 2C. Overall, major depressive disorder was present in 17% of patients, minor depression in 22%, and dysthymia in 13%. The prevalence of clinically significant depressive symptoms was 35%. While dysthymia may be diagnosed in the presence of major depressive disorder or minor depression (the concept of 'double depression'), it is surprising that none of the studies have looked at both minor depression and dysthymia at the same time.

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**Table 2A.** Reported prevalences (%) of major depressive disorder, minor depression, dysthymia, and clinically relevant depressive symptoms (Structured clinical interview)

Study	Sample	Sample size	Quality score	Major depressive disorder	Minor depression	Dysthymia	Clinically relevant depressive symptoms
<b>Structured clinical interview</b>							
Starkstein (1990) <sup>17</sup>	Outpatient clinic	105	5	21	20		41
Starkstein (1992) <sup>18</sup>	Outpatient clinic	92	5	20	21		41
Hantz (1994) <sup>7</sup>	Population	73	7	2.7			2.7
Starkstein (1996) <sup>19</sup>	Outpatient clinic/dementia	33	6	30		27	57
Liu (1997) <sup>20</sup>	Outpatient clinic	109	5	16.5		25.7	42.2
De Rijk (1998) <sup>21</sup>	Population	384	5	2.3		4.7	7.0
Starkstein (1998) <sup>22</sup>	Outpatient clinic	112	6	22		31.3	53.3
Leentjens (2000) <sup>23</sup>	Outpatient clinic	63	6	25			25
Leentjens (2000) <sup>24</sup>	Outpatient clinic	53	6	23			23
Anguenot (2002) <sup>25</sup>	Outpatient clinic	135	6	55.6		2.2	57.8
Naarding (2002) <sup>26</sup>	Outpatient clinic	85	6	23.5			23.5
Weintraub (2003) <sup>5</sup>	Outpatient clinic	77	6	20.8	13		33.8
Lauterbach (2004) <sup>27</sup>	Outpatient clinic	28	5	14.3		3.6	17.9
Nuti (2004) <sup>28</sup>	Outpatient clinic	90	6	21.1		18.8	39.9
Ertan (2005) <sup>29</sup>	Outpatient clinic	109	6	22.9	28.4		51.4
Papapetropoulos (2005) <sup>30</sup>	Brain bank data	67	7				43.3
Costa (2006) <sup>31</sup>	Inpatient clinic	58	5	20.7	34.5		55.2
Costa (2006) <sup>32</sup>	Inpatient clinic	83	6	21.7	25.3		47
Visser (2006) <sup>33</sup>	Outpatient clinic	92	6	19			19
Wichowicz (2006) <sup>34</sup>	Population	100	6	35			35

**Table 2B.** Reported prevalences (%) of major depressive disorder, minor depression, dysthymia, and clinically relevant depressive symptoms (Clinical interview)

Study	Sample	Sample size	Quality score	Major depressive disorder	Minor depression	Dysthymia	Clinically relevant depressive symptoms
<b>Clinical interview</b>							
Santamaria (1986) <sup>35</sup>	Outpatient clinic / recent onset	34	4	2.9		29.4	32.3
Mayeux (1988) <sup>36</sup>	Outpatient and inpatient clinic	339	4				47
Brown (1990) <sup>37</sup>	Outpatient clinic	40	6				25
Aarsland (1996) <sup>38</sup>	Population	235	6	7.7			7.7
Tandberg (1996) <sup>39</sup>	Population	245	6	7.7			7.7
Tandberg (1997) <sup>40</sup>	Population	245	6	7.7			7.7
Tandberg (1998) <sup>41</sup>	Population	239	6	7.8			7.8
Aarsland (1999) <sup>42</sup>	Population	235	5	7.2			7.2
Karlsen (1999) <sup>3</sup>	Population	233	6	7.7			7.7
Cubo (2000) <sup>43</sup>	Outpatient clinic	88	5	7.3			7.3
Giladi (2000) <sup>44</sup>	Outpatient clinic	172	5				33
Larsen (2000) <sup>45</sup>	Population	240	6	7.6			7.6
Krishnan (2003) <sup>46</sup>	Outpatient clinic	126	5				12.7

## MOOD & MOTIVATION IN PARKINSON'S DISEASE

**Table 2C.** Reported prevalences (%) of major depressive disorder, minor depression, dysthymia, and clinically relevant depressive symptoms (Rating scale)

Study	Sample	Sample size	Quality score	Major depressive disorder	Minor depression	Dysthymia	Clinically relevant depressive symptoms
<b>Rating scale</b>							
Mindham (1970) <sup>47</sup>	Inpatient psychiatric hospital	89	3				89
Tison (1995) <sup>48</sup>	Outpatient clinic and nursing home	60	6				32.7
Meara (1999) <sup>49</sup>	General Practice	132	5				64
Schrag (2000) <sup>1</sup>	General Practice	92	5				19.6
Happe (2001) <sup>50</sup>	Outpatient clinic	56	4				76.4
Schrag (2001) <sup>51</sup>	General Practice	97	5				19.6
Shulman (2001) <sup>52</sup>	Outpatient clinic	99	3				36
Happe (2002) <sup>53</sup>	Outpatient clinic	116	4				37.1
Marinus (2002) <sup>54</sup>	Outpatient clinic	177	4				38.4
Schrag (2002) <sup>55</sup>	General Practice	128	5				20
Shulman (2002) <sup>4</sup>	Outpatient clinic	101	3				44
Royo (2003) <sup>56</sup>	Outpatient clinic	353	4				56.9
Hely (2005) <sup>57</sup>	Outpatient clinic	52	4				53.6
Holroyd (2005) <sup>58</sup>	Outpatient clinic	100	4				15
Kang (2005) <sup>59</sup>	Population	193	5				13
Prado (2005) <sup>60</sup>	Outpatient clinic	60	4				38.3
Kirsch-Darrow (2006) <sup>61</sup>	Outpatient clinic	80	3				26.3
Weintraub (2006) <sup>62</sup>	Outpatient clinic	130	4				36.2
<b>Weighted mean</b>			<b>5.1</b>	<b>14</b>	<b>23</b>	<b>13</b>	<b>29</b>

The influence of setting on the prevalence of depressive disorders is shown in Table 3. For major depressive disorder, population studies report significantly lower prevalences than studies in outpatient samples ( $\chi^2 = 78.4$ ,  $df = 1$ ,  $p < 0.001$ ) and hospital inpatient settings ( $\chi^2 = 16.3$ ,  $df = 1$ ,  $p < 0.001$ ).

For the prevalence of clinically significant depressive symptoms, population studies also report significantly lower prevalences than studies in respectively general practices, outpatient settings, inpatient settings, and nursing homes ( $\chi^2 = 143.5$ ,  $df = 1$ ,  $p < 0.001$ ;  $\chi^2 = 288.6$ ,  $df = 1$ ,  $p < 0.001$ ;  $\chi^2 = 335.6$ ,  $df = 1$ , and  $p < 0.001$ ;  $\chi^2 = 27.2$ ,  $df = 1$ ,  $p < 0.001$  respectively). Studies in hospital inpatient settings report significantly higher prevalences than studies in the population, general practices, outpatient settings, and nursing homes ( $\chi^2 = 335.6$ ,  $df = 1$ ,  $p < 0.001$ ;  $\chi^2 = 9.8$ ,  $df = 1$ ,  $p = 0.002$ ;  $\chi^2 = 33.2$ ,  $df = 1$ , and  $p < 0.001$ ;  $\chi^2 = 9.4$ ,  $df = 1$ ,  $p = 0.002$ , respectively).

**Table 3.** Prevalence (%) of major depressive disorder and clinically relevant depressive symptoms in different settings

Population	Major depressive disorder		Clinically relevant depressive symptoms	
	Number of studies	Prevalence	Number of studies	Prevalence
General population	10	7.8	11	8.9
General Practice	0		4	32.8
Outpatient setting	16	21.7	31	38.5
Inpatient setting	2	21.3	4	54.4
Nursing home	0		1	32.7

The reported prevalence of major depressive disorder in studies using a (semi-) structured interview to establish DSM criteria ranges from 2.3 to 55.6% with a weighted mean of 19%. In studies using DSM criteria without a structured interview the prevalence rates of major depressive disorder ranges from 2.9 to 7.7% with a weighted mean of 7%.

Clinically significant depressive symptoms were present in 2.7 to 57.8% with a weighted mean of 33% in studies using a (semi-) structured interview, 7.3 to 47% with a weighted mean of 27% in studies using DSM criteria, and in 13 to 89% with a weighted mean of 42% in studies using a cut-off on a depression rating scale.

## 2.4 Discussion

This is the first extensive review of the prevalence of depressive disorders in PD that takes the different settings and diagnostic approaches of the various studies into account. It shows that the average prevalence of major depressive disorder in PD is 17%, which is substantial, but less than the prevalence rates that are usually quoted. Minor depression was present in 22% and dysthymia in 13% of PD patients. In PD patients in the general population these numbers are lower, while they are higher in hospital out- and inpatients settings. We could not confirm that the prevalence of major depression is lower when structured interviews are used as opposed unstructured clinical interviews to confirm diagnostic criteria, as is reported by others<sup>11</sup>. In this review, the use of structured interviews leads to higher prevalence rates.

Two earlier reviews on the prevalence of depression in PD have been published. Both were part of a more extensive review that also included the etiology and/or treatment of depression in PD as well. Both used a similar search strategy, but neither performed a quality assessment before including studies. In the study by Slaughter et al., that included 45 studies, the setting was not considered. Reported average prevalences of the 11 included studies that used diagnostic criteria were significantly higher than those of our review: 25% for major depressive disorder, 37% for minor depression, and

23% for dysthymia<sup>14</sup>. Clinically significant depression was present in 42% of PD patients. The discrepancy with our findings is probably due to the fact that seven of the eleven studies included in the review, were not included in our analysis because of an insufficient quality rating. Veazey et al. reviewed 16 studies and gave a range for prevalence rate depression of 7 to 76%<sup>15</sup>. In this review, the prevalence of major depressive disorder in studies that utilized clinical interviews to establish DSM criteria ranged from 7.3% to 32%; when self-report questionnaires were used the prevalence ranged from 27.3% to 76%. In community-based prevalence studies, the reported rate of MD was 7.7%. When populations of outpatients were used, the rates of MD ranged from 7.3% to 32%. It is not clear to the authors how a similar search strategy would yield so few studies. No (weighted) means were calculated.

This study has several limitations. First of all, the combined prevalence of clinically relevant depressive symptoms, which in this study is 35%, may have been influenced by the relatively large number of studies that have focused on major depression only. The fact that major depression may be superimposed on dysthymia (the concept of 'double depression') was not accounted for in some of the studies and may have lead to overdiagnosis. The exclusion of publications stemming from the same database is a strength of this review. However, although the authors have tried to identify such publications, we may not have been aware of them all. Another strength of this systematic review in comparison to other reviews is that articles are selected on basis of quality criteria, which at the same time could be seen as a limitation. The quality criteria used for inclusion are chosen by the authors and thus subjective. However, the criteria are consistent with general recommendations for evidence-based research. Because of this, several studies, reporting the prevalence of depression in PD, were excluded because they did not describe the diagnostic criteria used for PD or depression, or did not adequately describe the selection procedures used. In addition, the validity of rating scales used to diagnose depression and the appropriateness of the cut-off score may also be subject to criticism. Finally, any systematic review is influenced by the limitations of the included studies themselves. One such limitation is the fact that any possible influence of antiparkinsonian and psychopharmacologic medication on the prevalence rate of depressive disorder was not taken into account in most reviewed studies. Especially the fact that PD patients may be effectively treated with an antidepressant for their depressive disorder, and hence not be recognized as having suffered from depression may lead to underreport in this review.

In this review we aimed to determine the prevalence of depression in patients with PD across the range of clinical settings and diagnostic approaches. The average prevalence of major depressive disorder in PD is 17%, the prevalence of dysthymia is 13%, while minor depression occurs more frequently, in 22% of PD patients. Although these prevalences are lower than previously reported, this systematic review nevertheless confirms that depression is a common complication in patients with PD.

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## CHAPTER 3

### Assessment of depression in Parkinson's disease: the contribution of somatic symptoms to the clinimetric performance of the Hamilton and Montgomery-Åsberg depression rating scales

*Reijnders JSAM, Lousberg R, Leentjens AFG.  
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## Abstract

**Objective:** To assess the influence of somatic symptoms of the Hamilton Depression Rating Scale (HAMD) and Montgomery-Åsberg Depression Rating Scale (MADRS) on the clinimetric performance of these scales in patients with Parkinson's disease (PD).

**Methods:** A total of 224 patients underwent a protocolized mental status examination, consisting of the Structured Clinical Interview for DSM IV major depressive disorder (SCID-D), as well as the HAMD and MADRS. Sensitivity, specificity, positive, and negative predictive values for a range of cut-off scores were calculated for both rating scales and for modified versions of these scales in which all somatic items were eliminated. In addition, receiver operating characteristic curves were obtained for both the modified and unmodified scales.

**Results:** Elimination of the somatic items of depression from the HAMD and MADRS resulted in a reduced specificity of both the HAMD and the MADRS, and an increased sensitivity of the MADRS.

**Conclusion:** The authors recommend the full version of the HAMD and MADRS if used for diagnostic purposes; for screening purposes, the abbreviated version without somatic items can be used. Additional advantages of using full rating scales, with somatic items included, are that these provide more information on the severity of depression and allow for easier comparison across studies.

### 3.1 Introduction

Parkinson's disease (PD) is a neuropsychiatric disorder, characterized by both motor and non-motor symptoms. Depression is probably the most common non-motor symptom<sup>1</sup>. DSM IV defined major depressive disorder occurs in 17% of PD patients and minor depression in 22%<sup>2, 3</sup>. The recognition and assessment of major depressive disorder in PD patients is often difficult. Psychomotor slowing, masked facies, mental slowing, concentration difficulties, and sleep disturbances are symptoms that can occur both in PD and in major depressive disorder. Attribution of these symptoms to either PD or to major depressive disorder, as the DSM IV classification advises, is problematic. The process of symptom attribution often leads to the underdiagnosis of depression in PD, but at the same time there is a risk for overdiagnosis since the physical symptoms of PD may mimic symptoms of depression even in euthymic patients. As the most commonly used depression rating scales, such as the Hamilton Depression Rating Scale (HAMD) and Montgomery-Åsberg Depression Rating Scale (MADRS)<sup>4, 5</sup>, invariably incorporate a number of these physical items, many authors have expressed their concern that this may confound the assessment of depression in these patients<sup>6, 7</sup>. Moreover, the score on the HAMD may be significantly influenced by the type, onset, and severity of the motor features of PD<sup>8, 9</sup>.

Currently, this issue is resolved by adopting an 'inclusive' approach, which means that all symptoms are considered to be related to depression, regardless of their overlap with PD<sup>10, 11</sup>. Rather than interpreting symptoms, a correction for higher depression scores due to overlapping symptoms of depression and PD can be made by adjusting score ranges for defining clinically significant depression. This is also advised by a Movement Disorder Society task force<sup>11, 12</sup>.

Another possible approach to resolve this issue is adjusting the depression rating scales themselves. The HAMD and MADRS could perhaps be modified to smaller scales that lack somatic items, provided that these somatic items in PD do not contribute to the diagnostic performance in the evaluation of depression in PD. However, some somatic symptoms accompanying depression, especially reduced appetite and early morning wakening, have been shown to be more specific for depression than for PD<sup>13</sup>. The present study aimed at evaluating the influence of somatic items on the clinimetric performance of the HAMD and MADRS in patients with PD.

### 3.2 Patients and methods

As part of an ongoing research project on psychopathology in PD, 254 consecutive patients with primary PD, as defined by the clinical criteria of the United Kingdom Parkinson's Disease Society Brain Bank (UK-PDS-BB), were referred from the neurological outpatient department for a protocolized mental status examination<sup>14</sup>. This

examination consisted of the Structured Clinical Interview for DSM IV Depression (SCID-D), to confirm or reject the diagnosis of major depressive disorder as defined by the criteria of the DSM IV<sup>15</sup>. An inclusive approach to the diagnostic criteria was followed in accordance with recommendations of international task forces<sup>10, 11</sup>. The DSM IV diagnosis of major depressive disorder was considered the gold standard in this study. Patients fulfilling the DSM IV criteria for dementia, assessment based on an unstructured clinical interview, were excluded in order to prevent unreliable answers due to recollection bias (n=30). All patients completed the 17-item HAMD, irrespective of the absence or presence of depression<sup>4</sup>. Of 154 patients, the score on the MADRS was also available<sup>5</sup>. Physical disability was rated according to the Hoehn and Yahr (H&Y) staging system; the cognitive status of the patients was assessed with the Mini Mental State Examination (MMSE)<sup>16, 17</sup>. All interviews and scales were administered by trained staff. Receiver operating characteristic (ROC) curves were obtained for both the HAMD and the MADRS<sup>18</sup>. This curve plots the 'sensitivity' versus '1 minus specificity' for every possible cut-off point. For both scales, two curves were obtained: one curve for the full rating scale, including all somatic items, and one for a modified version of the scale in which the somatic items had been eliminated. In the modified HAMD, the following items were eliminated (item number between parentheses): disturbances of sleep (4-6), psychomotor slowing (8), physical anxiety (11), reduced appetite (12), fatigue (13), reduced sexual interest (14), and weight loss (16). In the modified MADRS, the following items were eliminated: sleep disturbances (4), reduced appetite (5), and fatigue (7). Concentration difficulties (6), being an important overlapping symptom in PD and depression, was also eliminated. The clinimetric performance of both versions of the rating scales was compared by calculating their respective areas under the curve (AUCs). A larger AUC means a better clinimetric performance and a better dichotomization of the population according to the gold standard.

Maximal discrimination between non-depressed and depressed PD patients is reached at the cut-off point that has the highest sum of sensitivity and specificity, the so-called Youden index<sup>19</sup>. The sensitivities and specificities of these optimal cut-off points were compared<sup>20</sup>. Due to sample size requirements, a Fisher's Exact Test was used to compare the sensitivities and specificities of the full and the modified scales. All analyses were performed with SPSS version 15.0 (SPSS, Chicago). Statistical comparisons of ROC curves were done with StAR Software<sup>21</sup>.

### 3.3 Results

Of the 254 referred patients, 30 (11.8%) were excluded because of dementia. In the analysis of HAMD items, 224 patients participated: 135 men and 89 women, with an average age of 65.6 years (SD 10.4). Their average MMSE score was 27.7 (SD 2.3). According to the H&Y scale, 17 patients were classified as Stage I, 129 as Stage II, 55 as Stage III, 11 as Stage IV, and none as Stage V (12 patients were not classified). Thirty-eight patients met the DSM IV criteria for major depressive disorder (17.0%). The average HAMD score was 7.4 (SD 3.8) for non-depressed patients and 16.9 (SD 4.8) for depressed patients. Independent sample t tests showed that there were no significant differences between the depressed and non-depressed patients for age, H&Y, and MMSE score ( $t(222) = -1.24$ ,  $p = 0.215$ ;  $t(222) = 0.80$ ,  $p = 0.424$ ;  $t(222) = 1.48$ ,  $p = 0.142$ , respectively).

In the analysis of MADRS items, 154 patients participated, 92 men and 62 women, with an average age of 66.3 (SD 10.8). Their average MMSE was 27.7 (SD 2.1). According to the H&Y scale, 14 patients were classified as Stage I, 84 as Stage II, 43 as Stage III, 11 as Stage IV and none as Stage V (2 patients not classified). Twenty-nine patients met the DSM IV criteria for major depressive disorder (18.8%). The average MADRS score was 8.9 (SD 5.4) for non-depressed and 20.2 (SD 8.1) for depressed patients. There were no significant differences between the depressed and non-depressed patients for age, H&Y, and MMSE score ( $t(152) = -0.60$ ,  $p = 0.549$ ;  $t(152) = 0.18$ ,  $p = 0.857$ ;  $t(152) = 0.61$ ,  $p = 0.542$ , respectively).

Sensitivity, specificity, positive, and negative predictive values for different cut-off scores are shown in Tables 1 and 2 for the full version and the modified version of the HAMD, and for the MADRS in Tables 3 and 4. For the HAMD-17, the optimal cut-off score is 9/10 with a Youden index 1.73 (sensitivity 0.98, specificity 0.75). A cut-off of 9/10 means that when a patient scores 9 or less he is not considered to be depressed, and when he/she scores 10 or more he/she is considered depressed. For the modified HAMD without the somatic items, the optimal cut-off score is 4/5 (Youden index 1.69: sensitivity 0.98, specificity 0.71). For the MADRS, the optimal cut-off score is 13/14 (Youden index 1.59: sensitivity 0.79, specificity 0.80). For the modified MADRS, without somatic items, the optimal cut-off score is 5/6 (Youden index 1.68: sensitivity 0.93, specificity 0.75).



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**Table 1.** Sensitivity, specificity, positive, and negative predictive values at different cut-off scores for the 17-item HAMD

Cut-off	8/9	9/10*	10/11	11/12	12/13	13/14	14/15	15/16	16/17
Sensitivity	1	0.98	0.92	0.84	0.79	0.74	0.63	0.61	0.50
Specificity	0.65	0.75	0.80	0.85	0.89	0.94	0.96	0.96	0.98
PPV	0.37	0.45	0.48	0.53	0.60	0.72	0.75	0.77	0.82
NPV	1	0.99	0.98	0.96	0.95	0.95	0.93	0.92	0.91

PPV: positive predictive value, NPV: negative predictive value

\* Maximum sum of sensitivity and specificity

**Table 2.** Sensitivity, specificity, positive, and negative predictive values at different cut-off scores for the modified HAMD (eight items)

Cut-off	3/4	4/5*	5/6	6/7	7/8	8/9	9/10	10/11	11/12
Sensitivity	0.97	0.98	0.87	0.76	0.58	0.50	0.40	0.32	0.32
Specificity	0.64	0.71	0.81	0.87	0.94	0.96	0.99	1	1
PPV	0.36	0.41	0.48	0.55	0.65	0.73	0.88	0.93	1
NPV	0.99	0.99	0.97	0.95	0.92	0.90	0.89	0.88	0.88

\* Maximum sum of sensitivity and specificity

**Table 3.** Sensitivity, specificity, positive, and negative predictive values at different cut-off scores for the MADRS (ten items)

Cut-off	9/10	10/11	11/12	12/13	13/14*	14/15	15/16	16/17	17/18	18/19
Sensitivity	0.93	0.86	0.79	0.79	0.79	0.72	0.69	0.66	0.55	0.52
Specificity	0.61	0.63	0.72	0.75	0.80	0.86	0.89	0.90	0.91	0.93
PPV	0.35	0.35	0.40	0.43	0.48	0.54	0.59	0.59	0.59	0.62
NPV	0.97	0.95	0.94	0.94	0.94	0.93	0.93	0.92	0.90	0.89

\* Maximum sum of sensitivity and specificity

**Table 4.** Sensitivity, specificity, positive, and negative predictive values at different cut-off scores for the modified MADRS (six items)

Cut-off	4/5	5/6*	6/7	7/8	8/9	9/10	10/11	11/12	12/13	13/14
Sensitivity	0.97	0.93	0.83	0.72	0.72	0.69	0.66	0.59	0.55	0.38
Specificity	0.69	0.75	0.79	0.82	0.86	0.90	0.91	0.94	0.98	0.98
PPV	0.42	0.47	0.48	0.49	0.54	0.62	0.63	0.71	0.84	0.79
NPV	0.99	0.98	0.95	0.93	0.93	0.93	0.92	0.91	0.90	0.87

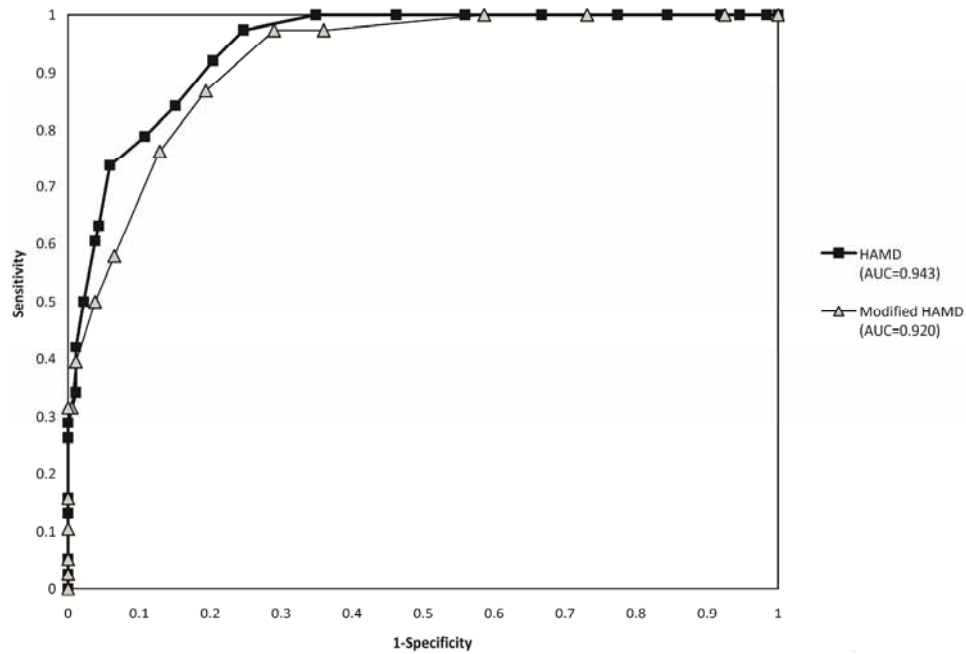
\* Maximum sum of sensitivity and specificity

The sensitivity of the HAMD at the optimal cut-off score (9/10) is 0.98. The sensitivity of the modified HAMD at the optimal cut-off score (4/5) was also 0.98. Comparisons of the specificity of the HAMD-17 (0.75) and the modified HAMD (0.71) at the optimal cut-off scores showed that the difference was statistically significant (Fisher's Exact Test,  $p > 0.0005$ ). Comparisons of the sensitivity and specificity of the MADRS (sensitivity 0.79, specificity 0.80) and the modified MADRS (sensitivity 0.93, specificity 0.75) at the optimal cut-off scores showed that the differences were also statistically significant (Fisher's Exact Test,  $p = 0.037$ ; Fisher's Exact Test,  $p > 0.0005$ ).

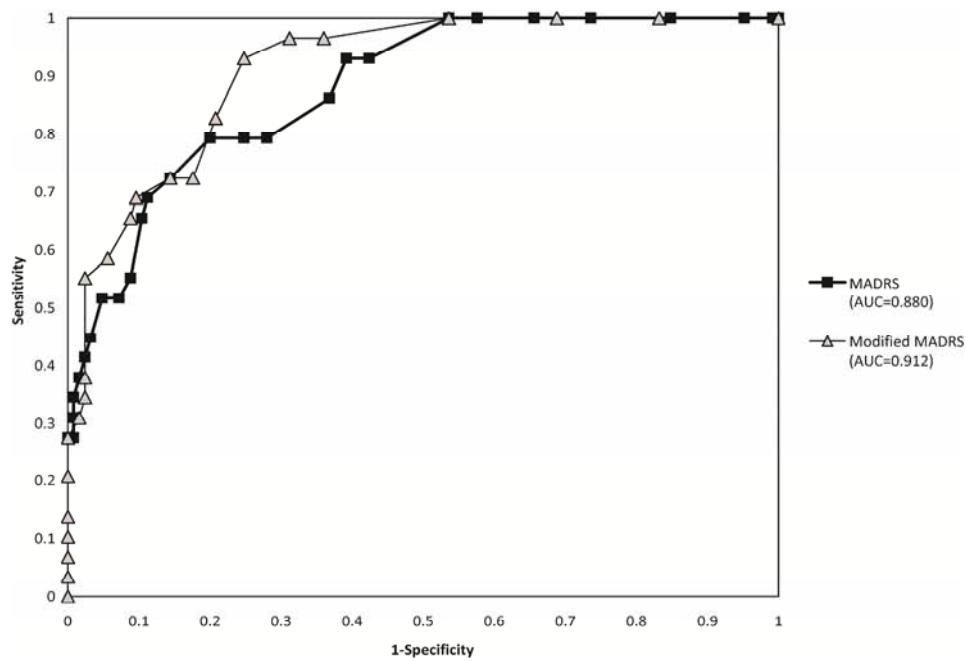
At the optimal cut-off score, the percentage correctly classified with the HAMD-17 is 79% and 75.5% with the modified HAMD. With the MADRS and modified MADRS, the percentage correctly classified at the optimal cut-off score is 79.8% and 78.5%, respectively.

Figure 1 shows the ROC curves of the HAMD. The AUCs for the HAMD with and without somatic items are 0.943 and 0.920, respectively. Comparisons of the two AUCs showed that the difference is not statistically significant ( $z = 1.82$ ,  $p = 0.069$ ). The ROC curves of the MADRS with and without somatic items are shown in Figure 2. The AUCs for the MADRS with and without somatic items are 0.880 and 0.912, respectively. Comparisons of the two AUCs showed that the difference is statistically significant ( $z = 2.14$ ,  $p = 0.033$ ).

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**Figure 1.** ROC curves of the 17-item HAMD and the modified HAMD without the somatic items



**Figure 2.** ROC curves of the full MADRS and the modified MADRS without the somatic items

### 3.4 Discussion

This study addresses the contribution of somatic items to the clinimetric performances of the HAMD and MADRS. Elimination of somatic items of depression from the HAMD did not result in a significant change of the AUC in patients with PD. Elimination of somatic items of depression from the MADRS resulted in a significant increase of the AUC. The ROC curves give us an indication of the overall clinimetric performance of the scales. However, we also looked more specifically at the influence of eliminating somatic items on the screening and diagnostic value of the scales. The sensitivity (screening value) of the HAMD of the optimal cut-off score remained the same after elimination of somatic items (0.98). The specificity (diagnostic value) of the optimal cut-off score showed a significant decrement after elimination of the somatic items (respectively, 0.75 with somatic items and 0.71 without somatic items).

For the MADRS, there is a significant increment of the sensitivity after elimination of the somatic items (respectively, 0.79 with somatic items and 0.93 without somatic items). The specificity of the optimal cut-off score significantly decreased after elimination of the somatic items (respectively, 0.80 with somatic items and 0.75 without somatic items).

Since our gold standard for depression, the DSM IV criteria of major depressive disorder, contains a number of somatic criteria that are also part of the HAMD and MADRS, elimination of these somatic items in the rating scales was expected to reduce the concurrent validity of these scales with the DSM IV criteria of major depressive disorder. The percentages correctly classified indeed showed a reduction after elimination of the somatic items.

A previous study, addressing the sensitivity of individual depressive symptoms of the HAMD and MADRS and their relative contribution to the diagnosis of major depressive disorder, showed that the somatic items of the MADRS had relatively low discriminative properties. With the HAMD, there were two somatic items, reduced appetite and early morning wakening, with relatively high discriminative properties<sup>13</sup>. Our study showed that excluding these somatic items with high discriminative properties from the HAMD did not result in a decrease of the sensitivity. A possible explanation for this is that patients included in our study had relatively few somatic symptoms.

Our study has several limitations. First of all, we investigated the influence of somatic items by using a gold standard (DSM IV diagnosis of major depressive disorder) which includes somatic items itself. A second limitation is that a cumulative database is used in this study. This means that patients were assessed by different staff members. A third limitation is that there may be confounding influences of comorbidity other than PD or by medication, which we did not take into account.

In general, depression rating scales should not be used for diagnostic purposes: a diagnosis requires the use of diagnostic criteria<sup>11</sup>. Eliminating somatic items from the HAMD and MADRS results in a reduced specificity of both scales and an increased

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sensitivity of the MADRS. This is why we recommend the full version of the HAMD and MADRS if used for diagnostic purposes; for screening purposes, the abbreviated version without somatic items can be used. However, generally self report scales are preferred for screening. Additional advantages of using full rating scales, with somatic items included, are that these provide more information on the severity of depression and allow for easier comparison across studies.

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The background of the page is a grayscale abstract image. It features several bright, diagonal light rays or streaks that intersect across the frame. In the lower-left quadrant, there is a bright, glowing, somewhat circular or oval shape that appears to be the source of some of the light rays. The overall effect is ethereal and dynamic.

## CHAPTER 4

### The association between motor subtypes and psychopathology in Parkinson's disease

*Reijnders JSAM, Ehrt U, Lousberg R, Aarsland D, Leentjens AFG.  
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## Abstract

**Background:** In Parkinson's disease (PD) it has been suggested that various motor subtypes are also characterized by a different prevalence and severity of specific non-motor symptoms such as cognitive deterioration, depression, apathy, and hallucinations. The aim of this study was to investigate the association between motor subtypes and psychopathology in PD.

**Methods:** An exploratory and confirmatory cluster analysis of motor and psychopathological symptoms was performed with a randomized sample of 173 patients each, stemming from two research databases: one from Stavanger University Hospital and one from Maastricht University Hospital. These databases contained data of standardized assessments of patients with the Unified Parkinson's Disease Rating Scale, the Montgomery-Åsberg Depression Rating Scale, and the Mini Mental State Examination.

**Results:** PD patients can be accurately and reliably classified into four different subtypes: rapid disease progression subtype, young-onset subtype, non-tremor-dominant subtype with psychopathology and a tremor-dominant subtype. Cognitive deterioration, depressive and apathetic symptoms, and hallucinations all cluster within the non-tremor-dominant motor subtype, that is characterized by hypokinesia, rigidity, postural instability, and gait disorder.

**Conclusions:** This study shows that non-tremor-dominant PD is associated with cognitive deterioration, depression, apathy, and hallucinations, which has implications for future research into the pathophysiology of psychopathology in PD.

## 4.1 Introduction

Parkinson's disease (PD) is increasingly considered a neuropsychiatric disorder, characterized by both motor and non-motor symptoms. Motor symptoms include hypokinesia, bradykinesia, rigidity, tremor, and postural instability. Non-motor symptoms include depression, apathy, cognitive deterioration, hallucinations, and sleeping disorders. Non-motor symptoms are responsible for a considerable reduction in quality of life <sup>1</sup>. Depression is the most common neuropsychiatric disturbance: major depressive disorder occurs in 17% of patients and minor depression in 22% <sup>2</sup>. Apathy is reported in 16.5% to 40% of PD patients <sup>3, 4</sup>. Dementia occurs in 24 to 31% and hallucinations in up to 40% <sup>5, 6</sup>.

The clinical presentation of the motor symptoms in PD may vary, and different subtypes have been described, such as a 'hypokinetic-rigid', a 'tremor-dominant', and a 'postural instability-gait disorder' form <sup>7, 8</sup>. Although clinically recognizable, these motor subtypes have not been the subject of extensive research. Moreover, it has been suggested that the various motor presentations of PD are also characterized by a different risk and severity of specific non-motor symptoms such as depression, apathy, and cognitive problems. A higher prevalence and severity of depressive symptoms has been described in the 'hypokinetic-rigid' group compared to the 'classic' (tremor plus rigidity and/or bradykinesia) PD group <sup>9</sup>. Other studies have reported that PD characterized by postural instability and gait difficulty (PIGD) is associated with a faster rate of cognitive decline <sup>10, 11</sup>.

Our goal is to establish different subtypes in a large and diverse sample of PD patients and also to validate the cluster solution by performing a confirmative cluster analysis.

## 4.2 Method

A total of 350 patients with PD as defined by the Queens Square Brain Bank criteria participated in the analysis <sup>12</sup>. To this end, two databases, containing epidemiological data of standardized assessments using the same instruments, were combined to increase sample size. One database was from a population based study of Stavanger University Hospital and one from an outpatient based study of Maastricht University Hospital. The instruments included in the standardized assessment were the Unified Parkinson's Disease Rating Scale (UPDRS) <sup>13</sup>, the Montgomery-Åsberg Depression Rating Scale (MADRS) <sup>14</sup>, and the Mini Mental State Examination (MMSE) <sup>15</sup>.

Patients from the combined database were randomly assigned to one of two samples. The first sample was used for an exploratory (K-means) cluster analysis <sup>16</sup> and the second sample for confirmation of these clusters. The variables used in the exploratory cluster analysis are tabulated in Table 1.

**Table 1.** Variables used in the cluster analysis

<b>Motor variables</b>	
Tremor	Mean score of UPDRS items 16,20,21 <sup>8</sup>
Hypokinesia/rigidity	Mean score of UPDRS items 22,31
Postural instability gait difficulty	Mean score of UPDRS items 13,14,15,29,30 <sup>8</sup>
L-dopa complications	UPDRS total score part IV
Disease progression	UPDRS total score part I,II,III / disease duration <sup>17</sup>
Age at disease onset	Age minus disease duration <sup>17, 18</sup>
<b>Psychopathology</b>	
Cognition	MMSE total score
Depression	MADRS total score
Apathy	UPDRS part I item 4
Hallucinations	UPDRS part I item 2

The actual number of clusters was decided during the analysis on the basis of the change of cluster distances between the successive steps and the clinical face validity of clusters. Identifying between 2 and 5 clusters was considered clinically useful in typing the spectrum of PD patients. In the successive cluster analyses, clusters were described on the basis of the differences in means of the variables included in the cluster solution. After that, an attempt was made to confirm the solution found in the exploratory cluster analysis in the second sample. Demographical and clinical characteristics such as age, disease duration, Hoehn & Yahr Rating scale<sup>19</sup> (H&Y), and score on the activities of daily life (ADL) (total score on UPDRS part 2) were used to validate and further specify the different clusters.

### 4.3 Statistical analysis

Comparison of populations between the two institutions was done with t-tests for continuous variables. A k-means cluster analysis was performed with the standardized scores of the following variables (see Table 1): tremor, hypokinesia/rigidity, PIGD, L-dopa complications, disease progression, age at disease onset, cognition, depression, apathy, and hallucinations. Discriminant-analytical techniques were used for the exploratory cluster analysis<sup>20</sup>. The chi-square technique was used to show the distribution of the two populations (Stavanger and Maastricht) between the identified clusters. For validation of the obtained cluster solution, one-way analysis of variance was used with post hoc multiple comparisons. All reported test results are two-tailed and a

P-value < 0.05 is considered significant. Analyses were performed with SPSS version 12.0 (SPSS, Chicago).

## 4.4 Results

### Demographical findings

The total sample consisted of 350 PD patients; 224 from Stavanger and 122 from Maastricht. Table 2 shows the differences in mean age, disease duration, H&Y, ADL, cognition (MMSE score), and depression (MADRS score) between patients from the two institutions. Patients from the Stavanger sample were older, had a longer disease duration, more cognitive symptoms, but less depressive symptoms than patients from the Maastricht sample.

The variables used in the explorative cluster analysis were standardized per institution, in order to control for possible institution-effect. There were four missing values which results in a total sample size of 346. Patients from the combined database were randomly assigned to one of two samples, each containing 173 PD patients. Independent sample t-tests showed that there were no differences between the two samples for age, disease duration, H&Y, ADL, cognition (MMSE score), and depression (MADRS score) ( $t(344) = 1.12$ ,  $p = 0.266$ ;  $t(344) = -1.56$ ,  $p = 0.121$ ;  $t(344) = 0.53$ ,  $p = 0.595$ ;  $t(344) = 0.79$ ,  $p = 0.432$ ;  $t(344) = -0.28$ ,  $p = 0.778$ ;  $t(344) = 0.54$ ,  $p = 0.592$ , respectively).

**Table 2.** Population characteristics of the two different institutions (Stavanger and Maastricht). Mean values (standard deviations) are given for age, disease duration, H&Y, ADL, cognition, and depression

	Stavanger (n = 224)	Maastricht (n = 122)	t-value	P-value
Age	73.2 (8.4)	65.3 (10.0)	-7.86	< 0.0005
Disease duration	9.0 (5.7)	6.7 (5.0)	-3.70	< 0.0005
H&Y	2.8 (1.0)	2.4 (0.8)	-3.45	< 0.0005
ADL (UPDRS part 2)	14.1 (8.5)	14.3 (5.9)	0.28	0.779
Cognition (MMSE total score)	25.0 (5.8)	27.7 (2.4)	4.99	< 0.0005
Depression (MADRS total score)	8.0 (6.3)	11.8 (7.2)	5.04	< 0.0005

H&Y: Hoehn & Yahr Rating scale; ADL: Activity of daily life; PIGD: Postural instability gait difficulty

### Explorative cluster analysis

The first sample (n=173) was used for an explorative cluster analysis. Patients were classified in four clusters, based on changes in cluster distances between successive

steps and the clinical face validity of the clusters. Table 3 shows the final cluster centers for the four clusters. The first patient profile (cluster 1) comprised 6.4% of the sample. Patients in this cluster are characterized by a rapid disease progression (UPDRS total score/disease duration). Besides this, the patients scored high on non-tremor-dominant motor symptoms and low on psychopathological measures. The patient profile is typed as 'rapid disease progression'. Cluster 2 comprised 29.4% of the sample. The patients in this cluster have a relative low age at disease onset, compared to the patients in the other three clusters. The patients also scored high on levodopa complications. These patients are, therefore, described as 'young-onset'. The third patient cluster comprised 16.8% of the sample. These patients scored high on the hypokinetic-rigid and PIGD motor symptoms and also on the psychopathological measures. The third cluster is, therefore, typed as 'non-tremor-dominant and psychopathology'.

The fourth patient profile is the largest cluster with 47.4% of the sample. The patients in this cluster are characterized by having tremor-dominant motor symptoms and low scores on psychopathological measures. This cluster is, therefore, typed as 'tremor-dominant'.

A chi-square test showed that there is no association between the two institutions (Stavanger and Maastricht) and the four clusters ( $\chi^2(3) = 0.58$ ,  $p = 0.902$ ). This means that cluster membership is independent of institution. For clarification, the unstandardized mean values and standard deviations of the variables used in the cluster analysis are shown in Table 4.

**Table 3.** Final cluster centers (N=173); variables that highly load within a certain cluster are shown in bold italics

	Cluster			
	1	2	3	4
Zscore: Tremor	-,17	-,48	-,34	<b>,19</b>
Zscore: Hypokinesia/rigidity	,48	-,06	<b>,91</b>	-,53
Zscore: PIGD	,31	-,12	<b>1,06</b>	-,43
Zscore: L-dopa complications	-,22	<b>1,04</b>	,01	-,53
Zscore: Disease progression	<b>2,37</b>	-,51	-,03	-,14
Zscore: Age at disease onset	,71	<b>-,97</b>	,15	,21
Zscore: Cognition	-,21	,49	<b>-1,52</b>	,32
Zscore: Depression	-,07	,31	<b>,99</b>	-,61
Zscore: Apathy	-,05	-,05	<b>,95</b>	-,52
Zscore: Hallucinations	-,22	-,17	<b>1,21</b>	-,27

PIGD: Postural instability gait difficulty

### Confirmation of the explorative cluster analysis

To establish classification accuracy the four clusters determined by the explorative k-mean cluster analysis were compared with their cluster assignment determined by a classification model. The classification model used was based on measures of multivariate generalized squared distances and on Bayesian posterior probabilities<sup>16, 21</sup>. The mean posterior probability of sample 1 patients being assigned to cluster 1, 2, 3, and 4 was 0.96, 0.94, 0.96, and 0.95, respectively.

The cluster means and covariance matrices that were developed from the explorative cluster analysis of sample 1 were then used to classify patients in sample 2 into one of the four clusters. Patients were assigned to a specific cluster if the following decision rules were met: their posterior probability of belonging to the cluster was at least 0.66 and a chi-square test of their generalized squared distance from the cluster centroid was non-significant at the 0.05 level. The average posterior probability of group membership for the patients classified into cluster 1, 2, 3, and 4 were 0.89, 0.91, 0.94, 0.93, respectively, thus confirming the cluster solution.

### Validation of the cluster solution

To validate the cluster solution, variables not used to generate the cluster solution were used to test whether there were cluster differences. Demographical and clinical variables like age, disease duration, H&Y score, and ADL-score were used for validation in sample 1 (see Table 4). By comparing mean age among the four clusters, there were significant differences between the four clusters ( $F(3,169) = 15.02$ ,  $p < 0.0005$ ). Pairwise cluster comparisons indicated that cluster 2 patients have a significant lower mean age than patients from, respectively, cluster 1, 3, and 4 ( $t = -9.12$ ,  $p = 0.012$ ;  $t = -12.36$ ,  $p < 0.0005$ ;  $t = -8.09$ ,  $p < 0.0005$ ).

Disease duration showed significant differences between the four clusters ( $F(3,169) = 12.73$ ,  $p < 0.0005$ ). Pairwise cluster comparison indicated that patients from cluster 2 and 3 have significant higher disease duration than patients from cluster 1 and 4 ( $t = 8.17$ ,  $p < 0.0005$ ;  $t = 3.68$ ,  $p = 0.001$ ;  $t = 9.10$ ,  $p < 0.0005$ ;  $t = 4.60$ ,  $p = 0.001$ ).

Mean scores on the H&Y also showed significant differences between the clusters ( $F(3,169) = 28.28$ ,  $p < 0.0005$ ). Patients from cluster 3 have a significant higher (worse) average H&Y stage than patients in, respectively, cluster 1, 2, and 4 ( $t = 0.75$ ,  $p = 0.031$ ;  $t = 1.10$ ,  $p < 0.0005$ ;  $t = 1.48$ ,  $p < 0.0005$ ). Patients from cluster 4 have significant lower H&Y score than patients from cluster 1 and 2 ( $t = -0.72$ ,  $p = 0.019$ ;  $t = -0.38$ ,  $p = 0.033$ ).

The analysis of ADL-score was also significant different between the different clusters ( $F(3,169) = 22.38$ ,  $p < 0.0005$ ). Pairwise cluster comparison indicated that cluster 3 patients score significant higher (worse) on ADL in comparison to patients from, respectively, cluster 1, 2, and 4 ( $t = 6.07$ ,  $p = 0.029$ ;  $t = 9.15$ ,  $p < 0.0005$ ;  $t = 10.33$ ,  $p < 0.0005$ ).

Comparable results were found by using sample 2 instead of sample 1. The analysis on external variables provided evidence for the validation of the four clusters, showing that they are unique and distinct.

**Table 4.** Group characteristics for the four clusters. Mean values (standard deviations) are given for age, disease duration, H&Y, ADL (UPDRS part 2), and the variables used in the explorative cluster analysis

	<b>Cluster 1: Rapid disease progression (n=11)</b>	<b>Cluster 2: young-onset (n=51)</b>	<b>Cluster 3: Non tremor- dominant &amp; psycho- pathology (n=29)</b>	<b>Cluster 4: tremor- dominant (n=82)</b>
Age	72.5 (9.0)	63.3 (10.5)	75.7 (7.7)	71.4 (7.8)
Disease duration	2.6 (1.3)	10.8 (5.1)	11.7 (7.1)	7.1 (5.1)
H&Y	3.0 (1.2)	2.6 (0.6)	3.7 (0.8)	2.2 (0.7)
ADL	15.7 (5.3)	12.6 (5.7)	21.8 (6.7)	11.5 (6.0)
Tremor	0.9 (0.6)	0.6 (0.6)	0.7 (0.8)	1.1 (0.8)
Hypokinesia/rigidity	1.9 (0.5)	1.4 (0.6)	2.2 (0.8)	1.1 (0.6)
PIGD	1.3 (0.5)	0.9 (0.6)	1.9 (0.6)	0.7 (0.6)
L-dopa complications	1.8 (3.5)	5.8 (4.0)	2.5 (2.5)	0.7 (0.8)
Disease progression	21.3 (17.5)	3.9 (2.4)	5.9 (2.6)	5.9 (4.1)
Age at disease onset	69.9 (8.2)	52.6 (9.4)	64.0 (8.4)	64.3 (7.6)
Cognition (MMSE total score)	24.0 (4.7)	28.2 (1.8)	17.4 (7.7)	27.7 (2.3)
Depression (MADRS total score)	8.7 (5.2)	11.5 (6.7)	15.7 (6.4)	5.3 (4.2)
Apathy (UPDRS item 4)	1.1 (0.7)	1.1 (0.9)	2.0 (0.8)	0.6 (0.7)
Hallucinations (UPDRS item 2)	0.4 (0.7)	0.4 (0.6)	2.0 (0.8)	0.6 (0.7)

H&Y: Hoehn & Yahr Rating scale; ADL: Activity of daily life; PIGD: Postural instability gait difficulty

## 4.5 Discussion

In this study, we have identified four subtypes of PD: a rapid disease progression group, a young-onset group, a non-tremor-dominant group characterized also by non-motor comorbidity, and a tremor-dominant group. Two earlier studies have performed cluster analyses to establish different subgroups of PD patients. Graham and Sagar (1999) performed a cluster analysis with 176 PD patients and revealed three distinct subtypes; motor only subtype, motor and cognitive subtype, and rapid progression subtype<sup>18</sup>. Lewis et al. (2005) used a sample of 120 early PD patients, which revealed four subgroups; young disease onset group, tremor-dominant group, non-tremor-dominant

significant levels of cognitive impairment and mild depression and a rapid disease progression group <sup>17</sup>. The groups identified in our study are in agreement with the study of Lewis (2005).

Further validation of these motor groups was done with demographical and clinical variables that were not used in the original cluster analysis. The non-tremor-dominant group is characterized by a higher age and more severe motor symptoms. These factors have previously been associated with cognitive decline in PD <sup>11</sup>. Moreover, bradykinesia <sup>22</sup> and postural instability gait difficulty are also associated with cognitive decline <sup>10, 11</sup>.

Apart from cognitive problems, depressed mood, apathy, and hallucinations cluster with the non-tremor-dominant motor symptoms. This is in line with the study of Starkstein et al. (1998) and Buchwald et al. (2007), who reported higher prevalences of depressive symptoms in the hypokinetic-rigid group <sup>9, 23</sup>. No study has yet reported on a relation of apathetic symptoms to one of the motor presentations of PD. Several studies have associated hallucinations with more severe motor symptoms, but no association with a specific motor subtype was reported <sup>6, 24, 25</sup>. Previously a relation between hallucinations and cognitive decline was reported, which is confirmed in our study <sup>26-28</sup>.

One advantage of our study is that it has a larger sample size than the previous studies. This enabled us to not only perform an exploratory cluster analysis, but also a confirmatory analysis. In addition, it enabled us to include more psychopathological variables. Our study also has several limitations. First of all, population characteristics of the Stavanger and Maastricht sample turned out to be different. This is probably due to the different settings of the study. The Stavanger study was population based, while the Maastricht study was outpatient based. Patients referred to a (academic) hospital tend to be younger with a lesser disease duration. In order to avoid between-group differences between the samples used for exploratory and confirmatory analysis, data were standardized and patients from both institutions were randomly assigned to either one of the samples. Post hoc, it was shown that the cluster solution was independent of the institution. A second limitation is that the psychopathological symptoms 'apathy' and 'hallucinations' were assessed with individual items of the UPDRS. These items were not meant to, nor validated to be used outside the context of the respective full scale. A third limitation is sample size. Our sample size was such that a maximum of 10 variables could be included in the analysis. A larger size would have allowed us to include a larger number of variables, but the choice and number of variables to include is always subjective, and dependent on what is considered clinically relevant.

Since the underlying pathophysiology of the various subtypes is different, our findings may have implications for further research into the underlying pathophysiology of psychopathology in PD. In the hypokinetic-rigid more severe cell loss in the *ventrolateral* part of substantia nigra (SN) and dopaminergic loss in the posterior putamen has been described, which causes inhibition of the glutamatergic



thalamocortical pathway and reduced cortical activation. The tremor-dominant form is characterized by more severe cell loss in the *medial* SN, which project to the dorsolateral striatum and ventromedial thalamus, causing hyperactivity of thalamomotor and cerebellar projections<sup>29, 30</sup>. If specific psychopathological symptoms are related to specific motor symptoms, it may be assumed that the pathophysiology of these psychopathological symptoms will also be related to the affected pathways in this specific motor presentation.

Summarizing, our study shows that PD patients can be classified into four different subtypes with high accuracy and validity. These comprise a rapid disease progression group, a young onset group, a non-tremor-dominant group with psychopathology and a tremor-dominant group. Psychopathology, including depressed mood, apathy, hallucinations, and cognitive problems, clusters with non-tremor-dominant motor symptoms. Our findings have important implications for further studies about the underlying differences in pathophysiology between the different subtypes.

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## MOOD & MOTIVATION IN PARKINSON'S DISEASE

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## MOOD & MOTIVATION IN PARKINSON'S DISEASE

The background of the page is a grayscale abstract image. It features several bright, diagonal light rays or streaks that intersect across the frame. In the lower-left quadrant, there is a large, bright, out-of-focus shape that resembles a stylized flower or a cluster of petals, with a very bright center. The overall effect is ethereal and artistic.

## CHAPTER 5

### Validation of diagnostic criteria for apathy in Parkinson's disease

*Drijgers RL, Dujardin K, Reijnders JSAM, Defebvre L, Leentjens AFG.  
Parkinsonism & Related Disorders.*

## Abstract

**Background:** Apathy is a common neuropsychiatric syndrome in Parkinson's disease (PD) that affects quality of life. Research into apathy has been hampered by a lack of broadly accepted diagnostic criteria. Recently, diagnostic criteria for apathy in neuropsychiatric disorders have been proposed, which to date have not been validated in PD.

**Aim:** To validate the proposed diagnostic criteria for apathy in PD.

**Design and methods:** In a cross-sectional study, outpatients with PD visiting a movement disorders clinic underwent a protocolized assessment of motor function, activities of daily living (ADL), cognition, and mood. In addition, the diagnostic criteria for apathy were administered as well as two apathy rating instruments: the Lille Apathy Rating Scale (LARS) and the apathy section of the Neuropsychiatric Inventory (NPI).

**Results:** Of the included patients 17.2% were diagnosed with apathy according to the criteria. Acceptability and internal consistency of the criteria was good, as was the concurrent validity with the LARS and apathy section of the NPI. Discriminant validity of the criteria with depression was moderate to good. All domains of criterion B (behaviour, cognition, emotion) contributed to the diagnosis of apathy, of which reduced goal-directed behaviour was the most frequently observed symptom.

**Conclusion:** The recently proposed diagnostic criteria for apathy are useful in clinical practice and in research with PD patients with and without cognitive impairment.

## 5.1 Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor and non-motor symptoms, including psychiatric and behavioural problems. Apathy is one of the most common neuropsychiatric syndromes in PD. Frequencies of 17 to 70% have been reported, depending on the population characteristics and assessment procedures<sup>1-3</sup>. In PD, apathy is associated with more severe cognitive deficits, more severe depressive symptoms, and a decreased quality of life<sup>4-6</sup>. In research as well as in clinical practice, apathy is increasingly seen as a syndrome on its own rather than as a symptom of some other disorder, such as dementia or depression<sup>7,8</sup>. To date, there is no effective treatment for apathy<sup>9</sup>.

Research into apathy has been hampered by a lack of generally accepted diagnostic criteria<sup>9</sup>. In 2008, a consensus meeting was held by the European Psychiatric Association (EPA), the European Alzheimer's Disease Consortium (EADC), the Association Française de Psychiatrie Biologique (AFPB), and invited experts from Europe, Australia, and North America, to propose consensus diagnostic criteria for apathy as a syndrome<sup>10</sup> (Table 1). These proposed diagnostic criteria have subsequently been validated in 306 patients suffering from a range of neuropsychiatric diseases including Alzheimer's disease (AD), mixed dementia, Mild Cognitive Impairment (MCI), PD, Schizophrenia, and major depressive episode<sup>11</sup>. In this study, the criteria were shown to have good acceptability, inter-rater reliability, and known-groups validity. The aim of the present study was to further validate these diagnostic criteria in a sample of patients with PD.

## 5.2 Methods

### Design

This cross-sectional cohort study was designed as an extension to a study into anxiety symptoms in PD<sup>12</sup>.

### Sample

One hundred and twenty-two patients from Lille University Medical Centre, Lille, France, and Maastricht University Medical Centre, Maastricht, the Netherlands, underwent a single assessment. All patients suffered from idiopathic PD according to the Queens Square Brain Bank criteria<sup>13</sup>. Patients were excluded if they suffered from neurodegenerative disorders other than PD, had a clinical diagnosis of Parkinson's disease Dementia (PDD) as defined by criteria of the Diagnostic and Statistical Manual (DSM IV) of mental disorders, or severe cognitive decline, operationalized as a score on



the Mini Mental State Examination (MMSE) < 23<sup>14, 15</sup>. The study was approved by the Medical Ethics Committee of both hospitals and patients gave informed consent before participation.

**Table 1.** Diagnostic criteria for apathy (Robert et al.<sup>10</sup>)

For a diagnosis of Apathy the patient should fulfil the criteria <b>A, B, C, and D</b>	
<b>A</b>	Loss of or diminished <b>motivation</b> in comparison to the patient's previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others.
<b>B</b>	Presence of at least one symptom in at least two of the three following domains for a period of at least four weeks and present most of the time.
	<b>Domain B1- Behaviour:</b>
	Loss of, or diminished, goal-directed behaviour as evidenced by at least one of the following:
	- Initiation symptom: loss of self-initiated behaviour (for example: starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices).
	- Responsiveness symptom: loss of environment-stimulated behaviour (for example: responding to conversation, participating in social activities).
	<b>Domain B2 - Cognition:</b>
	Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:
	- Initiation symptom: loss of spontaneous ideas and curiosity for routine and new events (i.e., challenging tasks, recent news, social opportunities, personal/family, and social affairs).
	- Responsiveness symptom: loss of environment-stimulated ideas and curiosity for routine and new events (i.e., in the person's residence, neighbourhood or community).
	<b>Domain B3 - Emotion:</b>
	Loss of, or diminished, emotion as evidenced by at least one of the following:
	- Initiation symptom: loss of spontaneous emotion, observed or self-reported (for example, subjective feeling of weak or absent emotions, or observation by others of a blunted affect).
	- Responsiveness symptom: loss of emotional responsiveness to positive or negative stimuli or events (for example, observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news).
<b>C</b>	These symptoms (A - B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.
<b>D.</b>	The symptoms (A - B) are not exclusively explained or due to physical disabilities (e.g., blindness and loss of hearing), to motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance (e.g., drug of abuse, a medication).

### Cognitive and behavioural assessment

In a single visit, motor, cognitive, affective, and other domains were assessed. Motor function was assessed with section 3 of the Unified Parkinson's Disease Rating Scale (UPDRS)<sup>16</sup>. Cognitive status and activities of daily living (ADL) were evaluated using the MMSE and the Lawton Instrumental ADL (IADL) scale<sup>14, 17</sup>. The presence of depressive

disorders as defined by the criteria of the fourth edition of the Diagnostic and Statistical Manual (DSM IV) of the American Psychiatric Association (APA) was assessed with the Mini International Neuropsychiatric Inventory (MINI, a structured interview for DSM disorders) sections A (depressive disorder), and B (dysthymia)<sup>15</sup>. Severity of depressive symptoms was assessed with the 17-item Hamilton Depression Rating Scale (HAMD)<sup>18, 19</sup>. Trained psychologists assessed the diagnostic criteria for apathy by means of an unstructured clinical interview. All criteria were individually questioned and additional information of the caregiver, if available, was used in the scoring procedure. Following criterion D of the diagnostic criteria, domain B1, reduced goal-directed behaviour, was only scored if it was thought not to be directly related to motor disability. For practical reasons, the raters were not blind to other assessment scales. In addition, two apathy instruments were administered: the Lille Apathy Rating Scale (LARS) and apathy section of the Neuropsychiatric Inventory (NPI)<sup>20, 21</sup>. The LARS consists of 33 items divided over 9 domains and 4 subscales, with a score range from -36 to +36 points, with positive scores indicating more severe apathy<sup>21</sup>. Since this study intends to validate a new gold standard for apathy, in the absence of another standard, the LARS and apathy section of the NPI were used to assess the concurrent validity of the diagnostic criteria. The NPI requires information from a caregiver. If this was not available, information was collected from the patient if this information, in the researcher's opinion, was reliable.

### Statistical analysis

All statistical analyses were conducted using the Statistical Package for the Social Sciences, version 16.0 (SPSS, Chicago). To identify differences in scores, Kruskal Wallis tests were used since none of the included variables were normally distributed. Chi-square-tests were used to compare proportions. The level of significance for all analyses was set at  $p < 0.05$ .

The percentage of missing data was thought to reflect acceptability, with  $< 5\%$  missing data considered acceptable. Cronbach's alpha was calculated as a measure of internal consistency, with  $\leq 0.70$  considered acceptable.

Concurrent validity of the diagnostic criteria with the LARS and the apathy section of the NPI was estimated by calculating Phi correlation coefficients. Apathy was defined here as score on the LARS of  $\geq -16$ <sup>21</sup> or as a score of  $\geq 4$  on the apathy section of the NPI. A correlation  $< 0.3$  was considered weak, a correlation between 0.3 and 0.5 moderate, between 0.5 and 0.7 fair, and  $> 0.7$  good. Known-groups validity was assessed by comparing average scores obtained by apathetic and non-aphetic patients on the LARS and the apathy section of the NPI, using a Kruskal Wallis test. Discriminant validity between the diagnostic criteria of apathy and those of major depressive disorder, as well as with the HAMD score and the score on the depression

section of the NPI, was also estimated by calculating Phi correlation coefficients. In this case, lower correlation coefficients were thought to reflect better discriminant validity. The frequency of each of the three domains of criterion B in apathetic and non-apathetic patients was reported and tested for differences by chi-square tests. The scores on subscales of the LARS in apathetic and non-apathetic patients were also compared and tested for differences with a Kruskal Wallis test. The relationship between the four sub-factors of the LARS (intellectual curiosity, emotion, action initiation, and self awareness) and the three domains of apathy (B1, B2, and B3) was examined using a point biserial correlation coefficient.

### 5.3 Results

#### Demographic characteristics

Demographic characteristics of the population and disease-related variables of apathetic and non-apathetic patients are shown in Table 2. The total sample consisted of 122 patients with an average age of 64.6 years, of which 41% was female. The two centers did not differ on any of the variables, except for the scores on the H&Y stage (both a median of 2 and range from 1 to 3;  $p < 0.001$ ), IADL scale (a mean score of 16.9 for patients from Lille and 19.7 for patients from Maastricht;  $p = 0.001$ ), and the LARS (a score of -24.6 for patients from Lille versus -22.2 for patients from Maastricht;  $p = 0.048$ ). However, these differences were small and not considered clinically relevant.

Patients meeting the diagnostic criteria for apathy scored significantly lower on the MMSE, and higher on the HAMD, the LARS and the apathy section of the NPI than non-apathetic patients. For the IADL score, a trend towards lower (worse) scores for apathetic patients was observed ( $p=0.059$ ).

**Table 2.** Demographic and disease-related characteristics of overall population and apathetic versus non-apathetic patients (standard deviation between brackets), as well as of the Lille and Maastricht population. Differences in values or proportions between the two participating centres were tested with Kruskal Wallis, except sex, which was tested with a Chi square test.

	Total popula- tion (N = 122)	Apathetic (N = 21)	Non- apathetic (N = 101)	p- value <sup>a</sup>	Lille (N = 62)	Maas- tricht (N = 60)	p- value <sup>b</sup>
Age	64.6 (8.5)	64.2 (8.7)	64.6 (8.5)	0.844	63.4 (8.1)	65.7 (8.7)	0.138
Female (%)	41	42,9	40.6	0.939	57	38	0.558
Disease duration	8.5 (5.6)	7.5 (5.7)	8.7 (5.6)	0.220	9.6 (6.3)	7.5 (4.6)	0.099
H&Y stage (median)	2 (3)	2 (3)	2 (3)	0.298	2 (3)	2 (3)	<0.001
UPDRS III	19.4 (8.0)	21.8 (7.0)	18.9 (8.2)	0.050	20.7 (9.3)	18.1 (6.2)	0.063
MMSE	28.2 (1.8)	27.2 (2.1)	28.5 (1.6)	0.010	28.0 (1.9)	28.5 (1.6)	0.150
IADL	18.2 (6.2)	21.4 (8.7)	17.6 (5.3)	0.059	16.9 (5.4)	19.7 (6.6)	0.001
HAMD	6.3 (5.8)	13.0 (6.9)	5.0 (4.4)	< 0.001	6.2 (6.2)	6.5 (5.3)	0.346
NPI apathy	1.6 (2.8)	6.4 (3.0)	0.6 (1.2)	< 0.001	2.0 (3.3)	1.2 (2.0)	0.392
LARS	-23.4 (7.8)	-11.7 (5.9)	-25.8 (5.7)	< 0.001	-24.6 (8.1)	-22.2 (7.3)	0.048

<sup>a</sup> comparison non-apathetic versus apathetic, <sup>b</sup> comparison Lille versus Maastricht

### Acceptability and internal consistency

There were no missing data for the diagnostic criteria for apathy. Cronbach's alpha was 0.88.

### Frequency of apathy and overlap with depression

Twenty-one of the 122 included patients (17.2%) met the diagnostic criteria for apathy. According to the MINI, eight of the 122 patients (6.6%) suffered from dysthymia and thirteen (10.7%) from major depressive disorder. Four patients (3.3%) out of the total population met the criteria for both dysthymia and apathy; seven patients (5.7%) had both major depressive disorder and apathy. This implies that one third (33.3%) of the 21 apathetic patients also had a depressive episode, while more than half (53.8%) of the 13 patients with a depressive disorder met the diagnostic criteria for apathy (Table 3).

**Table 3.** Number and proportion (%) of PD patients with depression and dysthymia that is classified as apathetic or non-apatetic following the diagnostic criteria

	Apathetic	Non-apatetic	Total
No depression	10 (8.2%)	91 (74.6%)**	101 (82.8%)
Major depressive disorder	7 (5.7%)	6 (5.0%)**	13 (10.7%)
Dythymia	4 (3.3%)	4 (3.3%)*	8 (6.6%)
Total	21 (17.2%)	101 (82.8%)	122 (100%)

\*  $p \leq 0.01$ , \*\*  $p < 0.001$ **Validity**

The concurrent validity between the diagnostic criteria of apathy and the LARS and apathy section of the NPI yielded a Phi correlation coefficient of 0.72 and 0.76, respectively ( $p = 0.01$ ). The percentage of agreement between the diagnosis of apathy based on the diagnostic criteria and based on cut-off scores on the apathy rating scales was 81% for the LARS and 86% for the apathy section of the NPI, respectively. Ninety-four percent of the patients who were not diagnosed as apathetic on basis of the diagnostic criteria were also classified as non-apatetic by the LARS, which is the same percentage as for the apathy section of the NPI (Table 4).

Discriminant validity between the diagnostic criteria for apathy and the diagnosis of depressive disorder, the HAMD and the depression section of the NPI was also assessed by Phi correlation. Both for the MINI as well as the depression section of the NPI, the correlations were 0.34 and 0.31, respectively (both  $p = 0.01$ ), indicating a fair correlation, and thus good discriminant validity. For the HAMD, the correlation was 0.54 ( $p = 0.01$ ), indicating a moderate correlation, and thus a moderate discriminant validity. Known-groups validity was assessed by comparing the scores of the apathetic and non-apatetic patients on the LARS and the apathy section of the NPI. Apathetic patients scored significantly higher than non-apatetic patients on both scales ( $p < 0.001$ ) (Table 2).

**Table 4.** Numbers and percentage agreement of apathy when diagnosed on the basis of diagnostic criteria of apathy or on the basis of cut-off scores on the apathy section of the NPI and the LARS

	<b>NPI <math>\geq 4</math> Yes</b>	<b>NPI <math>\leq 3</math> No</b>	<b>LARS <math>\geq -16</math> Yes</b>	<b>LARS <math>\leq -17</math> No</b>	<b>Total</b>
Apathetic	18 (86%)	3 (14%)	17 (81%)	4 (19%)	21
Non-apathetic	6 (6%)	95 (94%)	6 (6%)	95 (94%)	101
Total	24 (20%)	98 (80%)	23 (19%)	99 (81%)	122

### Subdimensions of apathy

Table 5 illustrates that all three domains of apathy described in criterion B contribute to the diagnosis of apathy. In apathetic patients, reduced goal-directed behaviour (B1) was the most frequently observed domain (95%), followed by reduced goal-directed cognition (B2, 86%) and reduced spontaneous emotion (B3, 52%). Of the 21 apathetic patients, 38.1% scores positive on all three domains of criterion B, 47.6% scored on domains B1 and B2 only, 9.5% on domains B1 and B3 only, and 4.8% on domains B2 and B3 only.

When comparing scores on the LARS domains and subscales between apathetic and non-apathetic patients, the apathetic group scored higher on all domains, except for the domains 'concern' and 'self awareness', and the 'self awareness' subscale (Table 6). When correlating the three subdomains of criterion B with the four dimensions of the LARS (intellectual curiosity, emotion, action initiation, and self awareness), criterion B1 (behaviour) correlated fair with the subscale 'intellectual curiosity', but only weak to moderate with the other subscales. Criterion B2 (cognition) correlated fair with the subscales 'intellectual curiosity', and 'action initiation', and only weakly with the other subscales. Criterion B3 (emotion) had only weak correlations with the subscales (Table 7).

**Table 5.** Frequency of the three domains of the B criterion of the diagnostic criteria for apathetic and non-apathetic patients

	<b>B1</b>	<b>B2</b>	<b>B3</b>	<b>Total</b>
Apathetic	95.2%	85.7%	52.4%	21
Non-apathetic	23.8%	12.9%	9.9%	101

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**Table 6.** Comparison of means between apathetic and non-aphetic patients on the domains and subscales of the LARS

	Apathetic (n=21)	Non-aphetic (n=101)	p-value <sup>a</sup>
Everyday productivity	-2.10 (1.87)	-3.21 (1.12)	0.003
Interest	0.19 (2.23)	-1.73 (1.40)	<0.001
Taking initiative	-1.05 (2.04)	-3.25 (1.16)	<0.001
Novelty seeking	-0.19 (2.04)	-2.78 (1.71)	<0.001
Motivation	-0.90 (2.45)	-3.21 (1.42)	<0.001
Emotional responses	-1.86 (1.82)	-3.23 (1.17)	<0.001
Concern	-2.52 (1.72)	-2.78 (1.38)	0.632
Social life	-0.62 (2.18)	-2.65 (1.43)	<0.001
Self awareness	-2.52 (2.11)	-2.99 (1.45)	0.574
Intellectual curiosity	-0.40 (1.03)	-2.61 (0.85)	<0.001
Emotion	-2.12 (1.08)	-3.01 (0.99)	0.001
Action initiation	-1.55 (1.43)	-3.25 (0.86)	<0.001
Self awareness	-2.52 (2.11)	-3.01 (1.44)	0.529

<sup>a</sup> Kruskal Wallis tests

**Table 7.** Correlation between subscales of the LARS and the three domains of criterion B of the diagnostic criteria for apathy (B1, B2, B3)

	Domain B1 Behaviour	Domain B2 Cognition	Domain B3 Emotion
Intellectual curiosity	0.557**	0.622**	0.346**
Emotion	0.236**	0.204*	0.327**
Action initiation	0.323**	0.466**	0.199*
Self awareness	0.157	0.281**	-0.013

\* correlation is significant at the 0.05 level (2-tailed), \*\* correlation is significant at the 0.01 level (2-tailed)

## 5.4 Discussion

This is the first study that validates the recently proposed diagnostic criteria for apathy in a population of patients with PD, with the aim of assessing their usefulness for clinical practice and research. Only one earlier study tested the criteria in patients with a range of neuropsychiatric diseases <sup>11</sup>. New instruments or criteria are generally validated against an existing gold standard. For apathy, no gold standard is available yet, which sets limitations to the assessment of clinimetric properties of the proposed criteria. While reliability can be assessed, assessing validity poses a problem, since this requires a gold standard. For assessment of concurrent validity and known-groups validity, the LARS and apathy section of the NPI were used as 'proxy gold standard'. The NPI is a frequently used instrument in neurodegenerative disorders (including PD), while the LARS was designed specifically for PD patients <sup>22</sup>. For both scales, we used proposed cut-off scores for apathy in accordance with those used in previous studies <sup>20-22</sup>. Our study shows that the diagnostic criteria for apathy have good internal consistency and acceptability. Strong correlations were found between the diagnostic criteria for apathy, and both the LARS and apathy section of the NPI, which implies good concurrent validity. Known-groups validity was also good. Discriminant validity of the apathy criteria to distinguish apathy and depressive disorder as diagnosed on the basis of the MINI was good. When discriminant validity of the criteria was assessed using the HAMD or depression section of the NPI as indicator of depression, this discriminant validity was good against the NPI depression section and moderate when the HAMD is used. A possible explanation for this difference is the fact that the HAMD considers some apathetic symptoms as part of the depressive symptomatology, with one item specifically asking about apathy. The depression section of the NPI does not have such items referring to apathy, since the NPI includes a separate apathy item.

In our study, 17.2% of the included patients were diagnosed with apathy on the basis of the diagnostic criteria. In the literature, the reported frequency of apathy varies from 17 to 70%, mostly on the basis of cut-off scores on a rating scale or assessment instrument <sup>1-3</sup>. Thus, the frequency found in this study is in the lower part of that range. One potential explanation for this may be the fact that we did not include patients with a clinical diagnosis of PDD, whereas the frequency of apathy is higher in patients with cognitive decline and dementia. This was supported in a recent study of Dujardin and colleagues in which 24.2% of the non-demented PD patients had apathy against 56.4% among the demented patients <sup>2</sup>. In an earlier validation study of the same criteria, a frequency of apathy of 27% in 44 PD patients was reported <sup>11</sup>. However, this study included PD patients with and without dementia. In line with our study, this latter study also suggests that the diagnostic criteria for apathy have a relatively higher threshold, when compared to cut-off scores on apathy rating scales.

All domains of the B criterion contributed to a diagnosis of apathy, with goal-directed behaviour being the most frequent reported domain. Domain 3, emotion, appears to



occur mostly in combination with one or both of the other two domains, which may be interpreted as an indication of more severe levels of apathy. In a post-hoc explorative analysis we could not confirm this hypothesis and results were inconclusive. The mean score on the apathy section of the NPI was significantly higher in patients meeting criterion B3 (8.2 versus 4.5;  $p = 0.005$ ), whereas the mean score on the LARS was not different for those that did or did not meet criterion B3 (10.9 versus -12.9;  $p = 0.75$ ).

Our study had several limitations. First of all, the included patients were recruited in two different centers. In both settings, different raters performed the assessment. For practical reasons, inter-rater reliability was not assessed as well were the raters not blind to other assessment scales. Another limitation is that patients with a diagnosis of PDD were excluded from the study while it is known that dementia predisposes to apathy<sup>1</sup>. Exclusion of these patients could give an underestimation of the frequency of apathy in PD and may explain the relatively low frequency of apathy found in this study. However, it underlines that in a clinical population of PD patients with and without cognitive decline, apathy is a quite frequent neuropsychiatric syndrome.

### Conclusion

This study shows good acceptability, internal consistency, concurrent, and known-groups validity of the proposed diagnostic criteria for apathy. In addition, discriminant validity with depression is moderate to good. All domains of criterion B contribute to the syndromal diagnosis, of which diminished goal-directed behaviour was most frequent. Lack of emotion is possibly related to a more severe level of apathy. These properties make the proposed criteria valid, and useful for clinical practice and research. The criteria provide a gold standard for studies into the epidemiology, symptomatology, pathophysiology, and treatment of apathy in patients with PD. Future studies have yet to examine the influence of cognitive functioning on the clinimetric properties of the diagnostic criteria.

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## CHAPTER 6

### Neuroanatomical correlates of apathy in Parkinson's disease: a magnetic resonance imaging study using voxel-based morphometry

*Reijnders JSAM, Scholtissen B, Weber WEJ, Aalten P, Verhey FRJ, Leentjens AFG.  
Movement Disorders.*

## Abstract

**Background:** Apathy is generally defined as a disorder of motivation and is considered one of the most common neuropsychiatric disturbances in Parkinson's disease (PD). Only few studies addressed the neuroanatomical correlates of apathy in PD.

**Aim:** To determine the structural correlates of apathy in PD patients.

**Methods:** Fifty-five PD patients underwent a neuropsychiatric and neuropsychological examination, and a 3 tesla magnetic resonance imaging scan was acquired. A voxel-based multiple regression analysis was used to calculate correlation between grey matter density and severity measures of apathy.

**Results:** Apathy correlates with decreased cognitive functioning and more depressive symptoms but not with more severe motor symptoms. High apathy scores were correlated with low grey matter density values in a number of cortical brain areas: the bilateral precentral gyrus (BA 4, 6), the bilateral inferior parietal gyrus (BA 40), the bilateral inferior frontal gyrus (BA 44, 47), the bilateral insula (BA 13), the right (posterior) cingulate gyrus (BA 24, 30, 31), and the right precuneus (BA 31).

**Conclusion:** Apathy in PD correlates with reduced grey matter density in a number of brain regions. The involvement of the cingulate gyrus and inferior frontal gyrus is in line with the results of earlier studies addressing apathy in patients with Alzheimer's disease or depressive disorder. Further studies addressing the pathogenesis of apathy are needed.

## 6.1 Introduction

Apathy is defined as a disorder of motivation and is considered one of the most common neuropsychiatric disturbances in Parkinson's disease (PD), occurring in up to 70% of patients <sup>1</sup>. Apathy is characterized by diminished motivation and effort to perform everyday activities, lack of intellectual interest and initiative regarding personal and social issues, and indifference or flattening of affect <sup>2-4</sup>. Although apathy overlaps with depression, several studies have shown that apathy and depression are different constructs <sup>5, 6</sup>. Apathy has been associated with decreased quality of life <sup>7</sup>, decreased performance on activities of daily living (ADL) <sup>7</sup>, and more severe cognitive dysfunction, more specifically executive dysfunction <sup>8-10</sup>. A recent study of Pedersen et al. (2009) reported that dementia and a more rapid decline in speech and axial impairment, features predominantly associated with dysfunction of non-dopaminergic subcortical structures, were independent risk factors for apathy in PD <sup>11</sup>.

The involvement of the prefrontal-basal ganglia system in apathy has often been hypothesized <sup>8, 12</sup>. There are only few studies addressing the neuroanatomical correlate of apathy in PD. Isella et al. (2002) studied the morphometric correlates of apathy in 26 PD patients but did not find any specific measure of frontotemporal atrophy correlating with severity of apathy <sup>5</sup>. A PET study of Remy et al. (2005) showed that apathy was inversely correlated with <sup>11</sup>C-RTI-32 binding (dopamine and noradrenaline) in the ventral striatum bilaterally <sup>13</sup>. Another PET study by Le Jeune et al. (2009) investigated apathy in PD patients after deep brain stimulation (DBS) of the subthalamic nucleus. They showed that postoperative apathy scores were correlated with decreased glucose metabolism in the bilateral posterior cingulate gyrus and left middle frontal gyrus <sup>14</sup>.

The objective of our study is to investigate the structural correlates of apathy, correlating the level of apathy with anatomical changes in grey matter density derived from magnetic resonance imaging (MRI) scans, as detected with voxel-based morphometry (VBM).

## 6.2 Methods

### Patients

Sixty consecutive outpatients with idiopathic PD, visiting the Neurology Clinic or the Memory Clinic of Maastricht University Medical Centre, were included. The diagnosis of idiopathic PD was established by use of the Queens Square Brain Bank criteria <sup>15</sup>. Exclusion criteria were neurological or psychiatric diseases other than PD, the use of psychopharmacological medication, abuse of alcohol and/or drugs, and cognitive deterioration, which was operationalized by a score of less than 24 on the Mini Mental State Examination (MMSE) <sup>16</sup>. Additionally, patients treated with DBS, or those meeting



MRI contra-indications, such as having a cardiac pacemaker, were excluded. All patients gave written informed consent before the study. The local Medical Ethics Committee of the Maastricht University Medical Centre approved the study.

### Assessment

All patients underwent a neuropsychiatric examination, a neuropsychological test battery, and a 3 tesla MRI scan on the same day. The neuropsychiatric examination included part 3 of the Unified Parkinson's Disease Rating Scale (UPDRS)<sup>17</sup> to measure the severity of motor symptoms, the Hoehn and Yahr staging scale (H&Y)<sup>18</sup> to assess disease stage, the 17-item Hamilton Depression Rating Scale (HAMD)<sup>19</sup> to measure depressive symptoms and the Neuropsychiatric Inventory (NPI)<sup>20, 21</sup> to assess the presence and severity of 12 neuropsychiatric disturbances (delusions, hallucinations, agitation, depressed mood, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behaviour, night-time behaviour disturbances, and eating abnormalities).

In addition the Apathy Evaluation Scale (AES-I)<sup>22, 23</sup> and the Lille Apathy Rating Scale (LARS)<sup>24</sup> were used to assess apathy. The LARS provides an overall apathy score and four composite subscores that presumably reflect four distinct dimensions of apathy: intellectual curiosity, action initiation, emotion, and self awareness<sup>25</sup>. Apathy was measured with three different scales in order to compare the results of these scales.

The neuropsychological test battery included the cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly part B (CAMCOG)<sup>26</sup> which incorporates the MMSE<sup>16</sup>. Subdomains in the CAMCOG are: attention, orientation, language comprehension, expression, memory, praxis, abstract reasoning, and perception.

### MR Imaging Data Acquisition

MRI scans were acquired with a 3.0 tesla Gyroscan NT MRI scanner (Philips Medical Systems, Best, the Netherlands). A coiled gradient was used, which provided high anatomical resolution and good grey/white matter contrast for subsequent segmentation. In addition to other MRI scan sequences, a T1-weighted three-dimensional isosurface scan (3D-ISO) was obtained for VBM analysis. The following parameters were used: voxel size: = 1 mm x 1 mm x 1 mm; TR = 8.1 ms; TE = 3.7 ms; TFE = 230 ms; flip angle = 8°; matrix = 224 x 224 pixels; FOV = 224 cm x 224 cm.

### Voxel-Based Morphometry

Image preprocessing was performed using Statistical Parametric Mapping 8 (SPM 8) (Wellcome Trust Centre for Neuroimaging, London). The first step was a 12-parameter affine registration with the Montreal Neurologic Institute <sup>27</sup> template as a target. The registered images were segmented into grey matter, white matter, and cerebrospinal fluid probability maps, using the SPM 8 segmentation priors. Registration accuracy of the grey matter probability maps was further enhanced by a registration method that uses alignment and scaling to spread the registration bias among the whole group. The transformation matrix is averaged by projection to a manifold, a method described in more detail in Karas et al. (2004) <sup>28</sup> and Woods et al. (2003) <sup>29</sup>. The registered grey matter volumes were smoothed using a Gaussian kernel filter set at 10 mm (full with half maximum) to reduce possible error from between-subject variability in local anatomy and render the data more normally distributed.

### Statistical analysis

The smoothed grey matter images were entered into a voxel-based multiple regression analysis to calculate linear correlations between grey matter density and severity of apathy assessed with different scales. More specifically, the LARS total score and four subscores for different domains of apathy (intellectual curiosity, action initiation, emotion, and self awareness), the AES total score, and the NPI apathy subscale were used in the analysis. Age, MMSE, and global grey matter volume were entered in this model as covariates for all variables. Global grey matter voxel intensity was included as a covariate to determine the regionally specific pattern of loss within the grey matter compartment, over and above global or generalized grey matter change. The threshold for statistical significance was set at  $p < 0.05$  corrected for multiple comparisons by false discovery rate correction; subsequently supra-threshold clusters were further filtered to  $p < 0.1$ , corrected for multiple comparisons.

The x, y, and z coordinates of areas with a significant correlation between grey matter density and scores on the apathy assessments were identified using the Talairach Daemon Client tool ([www.talairach.org](http://www.talairach.org)). An image of the average grey matter volume of the current population was used to map the significant results.

Statistical analysis of the behavioural data was performed using the Statistical Package for Social Sciences version 16.0 (SPSS, Chicago). Descriptive statistics were used to describe the demographical and clinical characteristics of the PD patients. Fisher Exact tests were used to compare proportions. Normality and linearity check was performed before Pearson's correlation coefficients were calculated to determine the relationships between the several apathy assessments and the demographical and clinical correlates. Correlation coefficients  $< 0.3$  (percent explained variance  $R^2$  of less than 9%) were considered weak; between 0.3 and 0.5 (percent explained variance between 9–25%) moderate; between 0.5 and 0.7 (percent explained variance between

25–49%) fair, and correlation coefficients  $> 0.7$  (percent explained variance more than 49%) were considered strong. P values  $< 0.05$  were considered significant.

### 6.3 Results

#### Demographical and clinical characteristics

A total of 60 PD patients were included in this study; 43 men (72%) and 17 women (28%). Because of movement artifacts, the MR images of 5 PD patients had to be excluded from the analysis, so the remaining sample size was 55 PD patients. None of the patients had a clinical diagnosis of PD dementia. Baseline characteristics are shown in Table 1 and indicate that PD patients included had mild to moderate PD motor symptoms and no clinically significant mood disorders. A fair percentage of patients scored above the cutoff for clinically relevant apathetic symptoms: 16.4% on the LARS (cutoff score -16/-17), 12.7% on the AES (cut-off score 37/38), and 32.7% on the NPI (frequency \* severity score 4 or higher). There were no associations between the proportion of patients on levodopa or dopamine agonist and clinically relevant apathetic symptoms as measured with the LARS, AES, and NPI ( $p = 0.473$ ,  $p = 0.360$ ,  $p = 0.584$ ,  $p = 0.211$ ,  $p = 0.640$ , and  $p = 0.168$ , respectively).

**Table 1.** Demographical and clinical characteristic of the included patients (N = 55)

	Mean (standard deviation)
Age	62.0 (10.1) range: 42-80
Education level*	4.0 (1.9)
UPDRS part 3	17.3 (4.9)
H&Y	median: 2 range: 1.5-3.0
Disease duration	6.6 (4.3)
HAMD	6.2 (3.4)
MMSE	27.8 (1.9)
CAMCOG	92.0 (7.0)
% on levodopa	62**
% on DA agonist	62**
LARS	-22.2 (6.8)
Intellectual curiosity	-2.0 (1.1)
Action initiation	-2.6 (1.1)
Emotion	-3.0 (1.1)
Self awareness	-2.9 (1.3)
AES	28.7 (6.0)
NPI	2.1 (2.3)

\* Education level ranging from primary education (1) to university degree (8)<sup>50</sup>, \*\* 35% of patients were using both levodopa and DA agonist. UPDRS: Unified Parkinson's Disease Rating Scale; H&Y: Hoehn and Yahr scale; HAMD: Hamilton Depression Rating Scale; MMSE: Mini Mental State Examination; CAMCOG: Cambridge Cognitive Examination; DA: dopamine; LARS: Lille Apathy Rating Scale; AES: Apathy Evaluation Scale; NPI: Neuropsychiatric Inventory

Correlation analyses were carried out with demographical and clinical variables, and with apathy scores (see Table 2). The LARS correlated moderately with age ( $r = 0.30$ ,  $p = 0.026$ ), HAMD ( $r = 0.36$ ,  $p = 0.007$ ), MMSE ( $r = -0.42$ ,  $p = 0.001$ ), and CAMCOG total scores ( $r = -0.49$ ,  $p < 0.000$ ). There were no significant correlations between the LARS score and disease duration or the UPDRS part 3 total score. Scores on the AES correlated moderately with MMSE ( $r = -0.32$ ,  $p = 0.016$ ) and CAMCOG total scores ( $r = -0.31$ ,  $p = 0.022$ ), but fair with HAMD total scores ( $r = 0.55$ ,  $p < 0.000$ ). There were no significant correlations with age, disease duration, and the UPDRS part 3 total score. The score on the apathy subscale of the NPI had a moderate correlation with the HAMD total score ( $r = 0.49$ ,  $p < 0.000$ ). No significant correlations were found between score on the apathy subscale of the NPI and age, disease duration, UPDRS part 3, MMSE, and CAMCOG total score.

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**Table 2.** Correlations between demographical variables, clinical variables, and apathy scores (assessed with the LARS, AES, and NPI)

	Age	Disease duration	UPDRS part 3	HAMD	MMSE	CAM-COG	LARS	AES	NPI
Age	-	0.18	0.23	0.05	-0.32*	-0.41*	0.30*	0.19	0.08
Disease duration		-	0.26	0.13	0.02	0.06	-0.10	-0.10	-0.03
UPDRS part 3			-	0.12	-0.16	-0.12	0.24	0.14	0.13
HAMD				-	-0.17	-0.06	0.36*	0.55*	0.49*
MMSE					-	0.75*	-0.42*	-0.32*	-0.06
CAM-COG						-	-0.49*	-0.31*	-0.17
LARS							-	0.83*	0.64*
AES								-	0.68*
NPI									-

\* Value is significant at  $P < 0.05$  (two-tailed). UPDRS: Unified Parkinson's Disease Rating Scale; HAMD: Hamilton Depression Rating Scale; MMSE: Mini Mental State Examination; CAMCOG: Cambridge Cognitive Examination; LARS: Lille Apathy Rating Scale; AES: Apathy Evaluation Scale; NPI: Neuropsychiatric Inventory

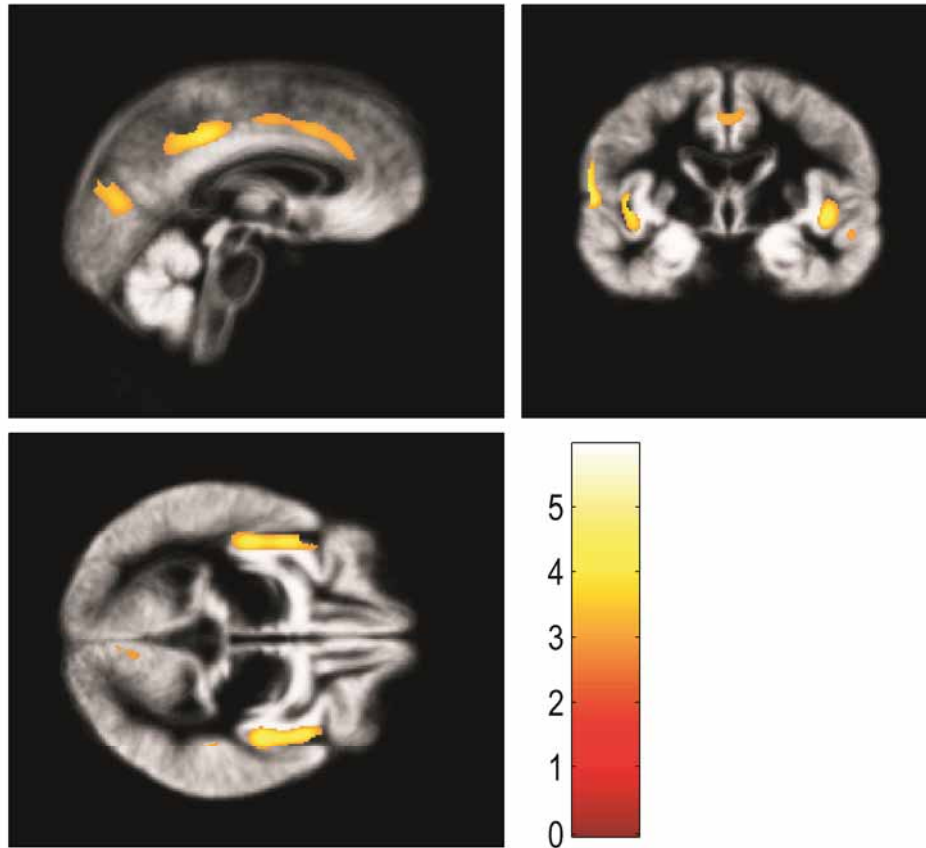
### Voxel-based multiple regression analysis

As shown in Table 3, the voxel-based multiple regression analysis showed significant correlations between grey matter density values and apathy scores on the LARS, AES, and NPI. High apathy scores on the LARS correlated with low grey matter density values in the bilateral precentral gyrus, the bilateral inferior parietal gyrus, the right precuneus, the bilateral insula, the bilateral inferior frontal gyrus, and the right (posterior) cingulate gyrus (see Figure 1). Looking at the four different subscales of the LARS (intellectual curiosity, action initiation, emotion, and self awareness) by four separate multiple regression models, no correlations between these subscales and low grey matter density values in distinct anatomical regions other than those mentioned above were observed. High apathy scores on the AES correlated significantly with grey matter density values in the left precentral gyrus, the bilateral insula, the bilateral inferior frontal gyrus, the left inferior parietal gyrus, and the right (posterior) cingulate gyrus. High apathy scores on the NPI correlated significantly with low grey matter density values in the left precentral gyrus, the bilateral insula, the bilateral inferior frontal gyrus, the left inferior parietal gyrus, and the right (posterior) cingulate gyrus.

**Table 3.** Brain regions showing a significant (negative) correlation between grey matter density values and apathy scores

Brain area	Cluster size	Right/Left	Brodmann area	MNI coordinate	Z-value at maximum
LARS					
Precentral gyrus	12598	L	6	-52 -8 37	5.13
Inferior parietal gyrus	5618	R	40	-44 -33 39	4.87
			4	44 -11 47	3.72
	5225	R	40	44 -30 35	4.12
Precuneus/			31	17 -63 27	4.17
Posterior cingulate gyrus	4596	R	30	8 -54 6	3.66
Insula			13	44 3 -2	4.18
Inferior frontal gyrus	3403	L	47	44 20 -1	4.15
			13	-44 14 3	4.14
	2649	R	47	-34 23 -11	3.37
Cingulate gyrus			24	2 -23 34	3.77
			31	12 -29 40	3.09
AES					
Precentral gyrus	6639	L	6	-52 -8 37	4.66
Inferior frontal gyrus	4080	R	44	-60 10 8	4.23
Insula			13	44 4 -2	4.27
Inferior frontal gyrus	3086	L	47	44 20 -1	4.32
			13	-44 14 3	4.21
	3004	L	47	-34 23 -11	3.45
Inferior parietal gyrus			40	-44 -33 39	4.75
Posterior cingulate gyrus	2807	R	31	17 -53 27	3.65
NPI					
Precentral gyrus	6165	L	6	-52 -8 36	4.54
Inferior frontal gyrus	3464	R	44	-60 10 8	4.39
Insula			13	44 3 -2	4.22
Inferior frontal gyrus	2674	L	47	44 19 -1	4.16
			13	-44 14 3	4.16
	2464	L	47	-34 23 -11	3.37
Inferior parietal gyrus			40	-44 -33 39	4.49
Posterior cingulate gyrus	2201	R	31	15 -54 18	3.43

LARS: Lille Apathy Rating Scale; AES: Apathy Evaluation Scale; NPI: Neuropsychiatric Inventory



**Figure 1.** Brain regions with significant negative correlation between grey matter density values and apathy scores measured with the Lille apathy rating scale. Visible are the right (posterior) cingulate gyrus, the right precuneus, the bilateral insula, and the left inferior parietal gyrus (SPM coordinates: 1.5; 6.5; -3.5)

## 6.4 Discussion

Our study shows that apathy occurs frequently in PD, but also that the exact frequency is dependent on the rating scale used to measure apathy. The prevalence of apathy was 16.4 % on the LARS, 12.7% on the AES, and 32.7% on the NPI. In line with previous studies<sup>5, 7-10</sup>, we found an association between apathy and cognitive dysfunction: higher apathy scores were correlated with lower MMSE and CAMCOG scores. Higher apathy scores also correlated with higher depression scores, as measured with the HAMD. Our study confirms previous findings showing no association between apathy and severity of motor symptoms or disease duration<sup>5, 8-10</sup>, although one recent community-based study of Pederson et al. (2008) did show a relationship between

apathy and more severe motor symptoms in PD patients. In this study that could be due to the large number of patients included with depression and dementia <sup>7</sup>.

The MRI data showed significant correlations between high apathy scores and low grey matter density values in a number of cortical brain areas: the bilateral precentral gyrus (BA 4, 6), the bilateral inferior parietal gyrus (BA 40), the bilateral inferior frontal gyrus (BA 44, 47), the bilateral insula (BA 13), the right (posterior) cingulate gyrus (BA 24, 30, 31), and the right precuneus (BA 31). Apathy was measured with three different apathy scales (LARS, AES, and NPI) in separate regression models, which showed consistent results. The four different subscales of the LARS (intellectual curiosity, action initiation, emotion, and self awareness) were also analyzed in separate regression models. The results showed no correlations between these subscales and low grey matter density values in distinct anatomical regions other than those resulting from the LARS total-score (see Table 3).

These results are in line with the PET study of Le Jeune et al. (2009) showing that higher scores on apathy rating scales were correlated with decreased glucose metabolism in the bilateral posterior cingulate gyrus <sup>14</sup>. Isella et al. (2002) did not find any specific measure of frontotemporal atrophy that correlated with severity of apathy <sup>5</sup>. In this particular study that could be due to small sample size or lack of sensitivity or accuracy of the morphometric linear technique used.

Functional and structural neuroimaging studies addressing apathy in Alzheimer's disease (AD) showed that apathy is associated with grey matter density loss in the (anterior) cingulate and the inferior frontal gyrus <sup>30-35</sup>. A pathological study of apathy in AD also showed a fair correlation between more severe apathy and an increased pathological burden in the anterior cingulate gyrus <sup>36</sup>. Lavretsky et al. (2007) examined the neuroanatomical correlates of apathy in older adults with and without major depression. Higher apathy scores were associated with decreased grey matter volume in the right anterior cingulate gyrus <sup>37</sup>.

To summarize, in line with previous studies in AD patients and depressive patients, we found evidence for involvement of the cingulate gyrus and the inferior frontal gyrus in apathy in PD as well. This stresses the stability of neural substrates of apathy across different pathologies.

Our results also showed associations between more severe apathy and low grey matter density in other areas: the premotor cortex, the bilateral insula, the right precuneus, and the bilateral inferior parietal gyrus. As the premotor cortex is involved in the initiation of voluntary movements, one could speculate that the grey matter density loss in this area may result in less initiative and motivation to initiate movements in PD patients with apathetic symptoms. As the insula plays a role in subjective emotional experience, grey matter density loss in this area may be related to loss of spontaneous emotion or emotional responsiveness, which is one of the characteristics of apathy <sup>38, 39</sup>. The parietal lobe plays an important role in integrating information from different senses and processes. Kjaer et al. (2002) hypothesized that the precuneus, the



inferior parietal gyrus, and the anterior cingulate gyrus constitute a functional network of reflective self-awareness<sup>40, 41</sup>. This network has previously been described to be impaired in apathy, although nowadays there is still a debate whether this is a dimension of apathy<sup>2</sup>. In addition, the inferior parietal gyrus has been linked to executive dysfunction in PD when assessed with the Frontal Assessment Battery<sup>42, 43</sup>. As apathy is associated with executive dysfunction<sup>44</sup>, one could hypothesize that executive dysfunction in apathetic PD patients is not only linked to frontal lobe dysfunction but also to parietal lobe dysfunction.

Levy and Dubois (2006) hypothesize that apathy can be described as the clinical consequence of disruption of the prefrontal-basal ganglia system. They differentiate three subtypes of disrupted processing: emotional-affective, cognitive, and auto-activation. Involvement of the cingulate gyrus and premotor cortex, as was shown in our study, indicates that auto-activation processing deficits could be associated with apathy in PD<sup>12</sup>.

Little is known about the neurochemical mechanisms of apathy in PD. A PET study of Remy et al. (2005) showed that the severity of apathy in PD patients was inversely correlated with <sup>11</sup>C-RTI-32 binding (dopamine and noradrenaline) bilaterally in the ventral striatum<sup>13</sup>. Czernecki et al. (2002) showed that levodopa treatment might improve motivation in some patients with PD, indicating that apathy in PD is at least partly a dopamine-dependent syndrome<sup>45, 46</sup>. Dujardin et al. (2007) suggested that nondopaminergic circuits participate in the pathophysiology of apathy in PD because the apathy level is mainly determined by cognitive impairment and not by association with the severity of motor symptoms. PD-specific pathology with multiple transmitter deficiencies in mesocortical monoaminergic systems may play a major role in the pathogenesis of apathy, including the mesocorticolimbic dopamine projection and the mesocortical noradrenergic and serotonergic projections<sup>8</sup>.

Our study has several limitations. First, sample size may not be large enough to detect small cerebral areas that are associated with apathy in addition to those detected in this study. Second, patients included in this study are characterized by only mild apathy scores and mild motor symptoms. Possibly, by including patients with more severe apathy, the contrast between groups may increase, resulting in significant correlations with other areas such as the basal ganglia or other limbic regions. Next, a correlational design instead of a between-groups design was used to study the structural correlates of apathy in PD. This was done because of the small sample size, the mild apathy scores, and the lack of consensus diagnostic criteria for apathy at the time of study inclusion. Finally, the VBM method used to analyze our MRI data has been criticized because of the risk of misregistration, caused by the spatial normalization procedure<sup>47, 48</sup>. In our study, registration accuracy was enhanced by alignment and scaling with an advanced registration method, spreading the registration bias among the whole group<sup>28, 29, 49</sup>. VBM has the major advantage of analyzing the whole brain and not be restricted by a priori assumptions about regions of interest.

## Conclusion

More severe apathy was correlated with decreased cognitive functioning and more severe depressive symptoms but not with more severe motor symptoms. This suggests that, in addition to dopaminergic systems, nondopaminergic systems may be involved as well. In line with previous studies in AD patients and depressive patients, we found evidence for involvement of the cingulate gyrus and the inferior frontal gyrus in the pathophysiology of apathy in PD. Our results will have to be confirmed by future structural and functional imaging studies investigating apathy in larger samples of PD patients. Moreover further studies are needed that specifically address the role of the dopaminergic and nondopaminergic systems in the pathogenesis of apathy, in the hope of revealing new treatment options.

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## **CHAPTER 7**

### **General discussion**



## MOOD & MOTIVATION IN PARKINSON'S DISEASE

This thesis addresses psychopathological symptoms in Parkinson's disease (PD). The main research goals were to identify patient subgroups and to address some diagnostic issues related to depression and apathy in PD. First, the main findings related to these research goals are discussed. Then some methodological issues are addressed. Finally, clinical implications and recommendations for future research are given.

## 7.1 Main findings and implications

### Identifying patient subgroups

Identification of clinical subgroups of patients has been the topic of previous research, but in these studies the focus has been on the classification of motor subtypes such as hypokinetic-rigid, tremor-dominant and postural instability-gait difficulty<sup>1-3</sup>. Our goal was to establish subgroups based on the full spectrum of clinical symptoms, including both motor and psychopathological symptoms. We were able to identify four subgroups of PD patients: a group with rapid disease progression, a young-onset group, a non-tremor-dominant group and a tremor-dominant group. The non-tremor-dominant subgroup was also characterized by cognitive deterioration, more severe depressive and apathetic symptoms, and more severe hallucinations (Chapter 4). Lewis et al. (2005) also investigated the heterogeneity of PD. Their study showed four subgroups, comparable to the ones we found; a rapid disease progression, a young disease onset, a tremor-dominant and a non-tremor-dominant with significant levels of cognitive impairment and mild depression<sup>4</sup>.

A note that has to be made is that the discrimination of subgroups described above, partly represents a discrimination of time of diagnosis, while other discriminations can only be made after a number of years of disease progression. This also indicates that patients assigned to a certain subgroup at a certain time point, can be assigned to another subgroup as time and disease progresses.

With the goal to confirm the classification of Lewis et al. (2005), a recent study of Selikhova et al. reviewed 242 donors with pathologically verified PD from the Queen Square Brain Bank for Neurological Disorders. Cases were segregated into the four subgroups described above. They found a strong association between a non-tremor-dominant disease pattern and cognitive disability. The non-tremor-dominant subgroup had a significantly higher mean pathological grading of cortical Lewy bodies and more cortical amyloid  $\beta$  plaque load than the other three subgroups<sup>5</sup>. This study shows that different clinical subgroups may have different pathological processes which in turn may have different aetiological bases. If this is indeed the case, this has important implications for clinical care and future research. Defining subgroups of patients with PD will then be useful in delineating the prognosis and therapeutic options.

Implications for clinical practice and research will be discussed in more detail at the end of this chapter.

### Diagnostic issues

This thesis focuses on diagnostic issues of two common neuropsychiatric symptoms in patients with PD: depression and apathy. One diagnostic issue is the recognition and assessment of depression in PD patients. The systematic review of prevalence studies of depression in PD (Chapter 2) showed weighted prevalence rates for major depressive disorder, minor depression, and dysthymia of 17%, 22%, and 13%, respectively. Clinically significant depressive symptoms are present in 35% of PD patients, indicating that depressive symptoms are common in PD patients. In contrast, prevalence rates of major depressive disorder based on standardized diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders) (DSM IV) are much lower. This may be due to the fact that strict DSM IV <sup>6</sup> criteria are difficult to use in PD and require attribution of specific symptoms to either PD or depression. Additionally, applying DSM criteria may miss a substantial number of patients with comorbid clinically significant depression. A workgroup from the National Institute for Neurological Diseases and Stroke <sup>7</sup> and the National Institute of Mental Health <sup>7</sup> has therefore issued the following recommendations: (1) an inclusive approach to symptom assessment to enhance reliability of ratings in PD and avoid the need to attribute symptoms; (2) anhedonia should only be diagnosed based on loss of pleasure rather than loss of interest (as it overlaps with apathy) for diagnosis of minor depression/subsyndromal depression, (3) elimination of the DSM exclusion criteria 'due to the effects of a general medical condition', (4) the inclusion of subsyndromal depression in clinical research studies; (5) the specification of timing of assessments for PD patients with motor fluctuations and the use of informants for cognitively impaired patients <sup>7</sup>.

Nevertheless, the contribution of somatic items to the diagnosis of depression in PD is still an issue of debate. We addressed this issue by investigating the influence of excluding somatic items from two depression rating scales on the clinimetric performance. The results (Chapter 3) showed that elimination of somatic items lead to a reduced specificity and unchanged sensitivity for the Hamilton Depression Rating Scale (HAM-D) <sup>8</sup> and a reduced specificity and increased sensitivity for the Montgomery-Åsberg Depression Rating Scale (MADRS) <sup>9</sup>. We therefore recommend the full versions of the two scales if used for diagnostic purposes, with adjusted cut-off scores for PD patients. For screening purposes, the abbreviated version without somatic items can be used. However, generally self report scales are preferred for screening. Additional advantages of using full rating scales, with somatic items included, are that these provide more information on the severity of depression and allow for easier comparison across studies.

Another diagnostic issue in diagnosing depression in PD is the considerable overlap between depression and apathy. Depressive patients often have symptoms of apathy; however apathy can occur in the absence of depression<sup>10-12</sup>. In our validation study (Chapter 5), 17.2% of the included PD patients met the diagnostic criteria for apathy, whereas 5.7% had both major depressive disorder and apathy. The reported prevalence of apathy is low, which could be due to the fact that only non-demented PD patients were included, whereas the frequency of apathy is higher in patients with cognitive decline and dementia<sup>13</sup>. Our results showed good concurrent validity between the diagnostic criteria of apathy and two apathy rating scales and fair discriminant validity between the diagnostic criteria of apathy and depression, measured by the DSM IV and the Neuropsychiatric Inventory (NPI)<sup>14</sup>.

It is yet unclear whether separate neural systems underlie depression and apathy. Depression in PD has been associated with grey matter decrease in the bilateral orbitofrontal, right temporal regions, and the limbic system<sup>15</sup>. In Chapter 6, we addressed the neuroanatomical correlate of apathy in PD, showing the involvement of the cingulate gyrus and inferior frontal gyrus. It could be hypothesized that orbitofrontal-subcortical connections underlie depression in PD, whereas inferior frontal-anterior cingulate subcortical connections underlie apathy in PD<sup>16, 17</sup>.

## 7.2 Methodological issues

### Diagnostic criteria

The diagnosis of PD was made with the help of operational criteria (see Appendix). In our studies, patients with idiopathic PD fulfilling the clinical criteria of the Queen Square Brain Bank were included<sup>18</sup>. We did not perform an additional diagnostic assessment with, for instance, IBZM or  $\beta$ -CIT single positron emission tomography (SPECT) in order to verify the diagnosis. This implies that some people may be incorrectly diagnosed with PD, whereas in fact they may suffer from other causes of parkinsonism. However, the operational criteria have a good diagnostic accuracy of 76%, when compared with post-mortem histological confirmation<sup>19</sup>.

To define major depressive disorder we used the DSM-IV of the American Psychiatric Association (APA)<sup>6</sup>. An inclusive approach was adopted by diagnosing depression in PD patients. The other recommendations of the NINDS/NIMH workgroup, described earlier, were also followed<sup>7</sup>.

In 2008, a consensus meeting was held between the Association Française de Psychiatrie Biologique (AFPB), the European Psychiatric Association (EPA), the European Alzheimer's Disease Consortium (EADC), and invited experts from Europe, Australia, and North America, to propose consensus diagnostic criteria for apathy as a syndrome<sup>20</sup> (see Appendix). These proposed diagnostic criteria have subsequently

been validated in 306 patients suffering from a range of neuropsychiatric diseases. In this study, the criteria were shown to have good acceptability, inter-rater reliability, and known-groups validity <sup>21</sup>. A validation study of these criteria in a population of PD patients is described in this thesis. Unfortunately, during data collection of other studies described in this thesis, the proposed criteria for apathy were not yet published. We therefore used rating scales to assess apathetic symptoms in PD patients.

### Rating Scales

In all studies presented in this thesis, rating scales were used, besides diagnostic criteria, to assess psychopathology and motor symptoms in PD (see Appendix). For assessment of depression, the HAMD and the MADRS were used. Both scales were reviewed by the Movement Disorder Society (MDS) task force and recommended for screening and assessment of severity of depression in PD <sup>22</sup>.

In Chapter 6, apathy was assessed with the Lars Apathy Rating Scale (LARS) <sup>23</sup>, the Apathy Evaluation Scale (AES) <sup>24</sup>, and the Neuropsychiatric Inventory (NPI). All three assessment scales were classified as 'suggested' by the MDS Task force <sup>25</sup>.

Most of the used rating scales are clinician-rated, except for the NPI (used in Chapter 6) which is based on caregiver's reports. In Chapter 6, we found a relative high percentage of patients with clinically relevant apathetic symptoms, measured with the NPI, in comparison to the LARS and AES. On the other hand, a study of Kinlay et al. (2008) reported lower frequencies of apathy based on caregiver reports in comparison to self-report <sup>26</sup>. Therefore, caution is needed when comparing frequencies of neuropsychiatric symptoms derived from self-reports and caregiver-reports.

To quantify motor symptoms of PD, we used the Unified Parkinson's Disease Rating Scale (UPDRS) <sup>27</sup>. This is the most frequently used and most thoroughly studied PD rating scale, with a good internal consistency, inter-rater reliability and criterion validity <sup>28</sup>. In Chapter 4, we also used items from the UPDRS mood and mentation section (section 1) to quantify psychopathological symptoms. The UPDRS has very recently been revised into a partly observer- and partly self-rated scale, named MDS-UPDRS <sup>29</sup>. The first section addressing non-motor symptoms has expanded from 4 to 13 items, stressing the importance of these symptoms in PD. For assessment of depression, the new version will focus only on mood to avoid ambiguities and overlap with symptoms of PD. Some of the somatic features of depression, as well as apathy, cognitive impairment, anxiety, and sleep disturbances, will be assessed in separate questions. The new version of the UPDRS should be used as a screening instrument for non-motor symptoms, an accompanying appendix will provide 'recommended' and 'suggested' scales for further evaluations.

### Study population

In the studies described in Chapters 3 and 6, PD patients were included who attended the psychiatric, neurological or movement disorder clinic of the Maastricht University Medical Centre. The study described in Chapter 4 included two different study samples. One study sample from a population based study of Stavanger University Hospital and one from an outpatient based study of Maastricht University Medical Centre. In the validation study described in Chapter 5, an outpatient study sample from Lille University Medical Centre was combined with an outpatient study sample from Maastricht University Medical Centre. In case of combined study samples, population differences were checked and reported.

The cohort of PD patients studied in this thesis mainly comprised patients in the early clinical stages of the disease (Hoehn & Yahr stages I-III), who were referred on a voluntary basis for participation in research studies. As can be seen from the relatively young mean age of the participants, this approach might have caused a selection bias. Although it must be stressed that these patients were recruited from various departments.

### Statistical methods used

Our statistical analysis included 'ordinary' descriptive statistics, chi-square tests (Chapters 2, 5), correlational statistics (Chapters 5, 6) and classification analysis (Chapter 3), but also more advanced statistical methods such as cluster analysis techniques (Chapter 4) and voxel-based morphometry (VBM) (Chapter 6).

Cluster analysis techniques were used to create homogeneous subgroups. In order to do this the average between-group distance is maximized and the average within-group distance is minimized. Subgroups are created in such a way that patients within a group share as many characteristics as possible, while at the same time differing as much as possible from patients in other groups. The choice of variables, patient characteristics, used to create the patient subgroups depends upon the researcher's theoretical background. A major strength of our study is that not only an explorative cluster analysis was done but also a confirmative analysis by which classification accuracy is proven.

In Chapter 6, VBM was used as an analyzing technique to examine the association between apathy and grey matter density in PD patients. One of the major advantages of this method is that the whole brain is analyzed at once, in contrast to region of interest (ROI) approaches. This is especially relevant when there are no a-priori assumptions of specific brain areas of interest, which was the case in our study of anatomical (grey matter density) correlate of apathy in PD. Although the structural correlates of apathy had been investigated in dementia. At present, no previous magnetic resonance studies (MRI) were done in PD populations. The VBM method gives a good indication of specific brain areas involved in apathy. This can (and should) then

be confirmed with studies using ROI approaches, analyzing methods which are much more time-consuming.

### 7.3 Clinical implications

Our findings have several clinical implications. Our cluster analysis, described in Chapter 4, showed that psychopathological symptoms (depression, apathy, cognitive deterioration, and hallucinations) all cluster together in one specific subgroup of PD patients. This finding has two important implications.

First, screening for psychopathology in PD patients belonging to this specific subgroup. Physicians should be more aware and screen more frequently for psychopathological symptoms when encountering patients with non-tremor-dominant motor symptoms like hypokinesia, rigidity, postural instability, and gait disorder. Related to this, there are known risk factors associated with specific psychopathological symptoms. For depression, family history of depression and right-sided onset of symptoms are risk factors<sup>30</sup>. For apathy, independent risk factors are dementia and a more rapid decline in speech and axial impairment<sup>31</sup>. Physician should be aware of these risk factors, to enhance early recognition of psychopathological symptoms.

Second, the treatment strategies applied to a patient are influenced by the subgroup the patient belongs to. Patients from the non-tremor-dominant subgroup are characterized by more severe psychopathological symptoms like depression and apathy. Many of these patients will already be on dopaminergic medication and/or require improvement of motor symptoms. The first step when encountering psychopathological symptoms would therefore be the optimization of existing treatment. Some dopaminergic agents that are used to treat the motor symptoms of PD have been advocated to have additional positive effects on mood, anhedonia, and motivation<sup>32-35</sup>. Another possibility could be cognitive behavioural therapy addressing a cognitive model of vulnerability to depression in PD patients<sup>36, 37</sup>.

As mentioned above, a frequent screening for psychopathological symptoms should be dependent on risk factors and the specific subgroup a patient belongs to. But it could also be argued that screening for a specific symptom should be dependent on the availability of treatment options. For example screening for cognitive impairment is important because pharmacological treatment options, in case of PD-dementia, are more effective in early stages than in later stages, when the patient would have noticed the symptoms himself. Screening for depression might also be useful because of the available treatment options. On the other hand, screening for apathy might be considered less useful because of the limited treatment options.

A diagnostic issue we described in this thesis is the difficulty of diagnosing depression due to overlap of depressive and PD motor symptoms. To enhance accurate diagnosis of depression, it is important to adopt the recommendations from the NINDS/NIMH

workgroup described earlier, like adopting a inclusive approach, elimination of the DSM exclusion criteria ‘due to the effects of a general medical condition’ and diagnosing anhedonia based on loss of pleasure rather than loss of interest <sup>7</sup>.

Another diagnostic issue is the overlap between depression and apathy. It may be difficult to distinguish depression from apathy when seeing a patient (or caregiver) who reports apathetic symptoms. The proposed diagnostic criteria, with good concurrent and fair discriminant validity, are therefore very important. It provides a diagnostic instrument that helps physicians to establish an accurate diagnosis.

Hopefully by addressing some of the diagnostic issues concerning depression and apathy in this thesis, the early recognition and diagnostic accuracy of these stressful symptoms will increase. Two last conditions, which are essential for early recognition and accurate diagnosis, are a close collaboration between neurologists and psychiatrists and an open interaction between patient/caregiver and their physician in which the patient/caregiver feels free to talk about the problems they encounters in their everyday life.

## 7.4 Further research

Based on the findings in the present thesis, some recommendations for further research can be formulated. The identification of the different subgroups of PD patients can be an important basis of further research. Functional imaging techniques, like positron emission tomography (PET) and functional MRI (fMRI), should be applied to these subgroups to reveal different aetiopathologies. We could hypothesize that a different constellation of neurotransmitter systems are involved in the etiology of the four subgroups. This can be investigated by using PET or SPECT imaging. If the involvement of various neurotransmitter systems is indeed different for the four subgroups, this could have important therapeutic possibilities. Nevertheless, further prospective research with longitudinal assessment of patients is needed to distinguish the variations and subgroups of PD and to show how these variations relate to progression.

With regard to the proposed diagnostic criteria for apathy. These criteria will provide an important contribution to clinical research of apathy, although the validity of these criteria in PD patients with dementia has to be examined yet.

Referring to the structural imaging study of apathy described in this thesis, there was a clear relation between grey matter atrophy in a number of cortical brain areas and symptoms of apathy. But understanding of the underlying neural networks is still lacking. Future research should try to gain more insight in these neural networks by combining structural with functional imaging techniques. Besides this, in our study only non-demented PD patients were included. New studies should investigate the



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structural correlates of apathy in demented PD patients in comparison with, e.g., apathy in Alzheimer's disease patients.

Finally, another area which urgently needs further research are the treatment options of apathy in patients with PD and other neurodegenerative diseases. Currently, there is limited and inconsistent evidence for the efficacy of any specific drug in treating apathy, although cholinesterase inhibitors and methylphenidate may be the best candidates for future randomized controlled trials<sup>38</sup>. Also non-pharmacological treatment options should be addressed in future studies. Hopefully this will lead to effective treatment options which will improve quality of life for both patient and caregiver.

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# **Appendix**

## **Diagnostic criteria and rating scales**

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This appendix gives an overview of the different diagnostic criteria for Parkinson's disease (PD), depression, and apathy and different rating scales, which were used in the studies presented in this thesis.

### **Queen square brain bank criteria for Parkinson's disease<sup>1, 2</sup>**

#### **Step 1: diagnosis of the parkinsonian syndrome**

- bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
- at least one of the following:
  - muscular rigidity
  - 4-6 Hz rest tremor
  - postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction

#### **Step 2: exclusion criteria for PD**

- history of repeated strokes with stepwise progression of parkinsonian features
- history of repeated head injury
- history of definite encephalitis
- oculogyric crises
- neuroleptic treatment at onset of symptoms
- more than one affected relative
- sustained remission
- strictly unilateral features after three years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of cerebral tumour or communicating hydrocephalus on CT scan
- Negative response to large doses of levodopa (if malabsorption excluded)
- MPTP exposure



**Step 3:** supportive prospective positive criteria for PD

- unilateral onset
- rest tremor present
- progressive disorder
- persistent asymmetry affecting side of onset most
- excellent response (70% - 100%) to levodopa
- severe levodopa-induced chorea
- levodopa response for five years or more
- clinical course of ten years or more

**DSM IV TR criteria for Major depressive disorder and Minor depressive episode<sup>3</sup>**

- A. Major depressive disorder: Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one symptom is either (1) depressed mood or (2) loss of interest or pleasure. Minor depressive episode requires only 2 of the 9 following symptoms for at least a two-week period.
- depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others
  - markedly diminished interest or pleasure in all, or nearly all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
  - significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day
  - insomnia or hypersomnia nearly every day
  - psychomotor agitation or retardation nearly every day
  - fatigue or loss of energy nearly every day
  - feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day
  - diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
  - recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
- B. The symptoms do not meet the criteria for a 'mixed episode'.
- C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

- E. The symptoms are not better accounted for by 'bereavement', i.e., after the loss of a loved one.

### **DSM IV TR criteria for Dysthymic disorder <sup>3</sup>**

- A. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 years.
- B. Presence, while depressed, of two (or more) of the following:
- poor appetite or overeating
  - insomnia or hypersomnia
  - low energy or fatigue
  - low self-esteem
  - poor concentration or difficulty making decisions
  - feelings of hopelessness
- C. During the 2-year period of the disturbance, the person has never been without the symptoms in A and B for more than 2 months at a time.
- D. No Major Depressive Episode has been present during the first 2 years of the disturbance.

### **Diagnostic criteria for Apathy <sup>4</sup>**

For a diagnosis of Apathy the patient should fulfill the criteria A, B, C, and D:

- A. Loss of or diminished motivation in comparison to the patient's previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others.
- B. Presence of at least one symptom in at least two of the three following domains for a period of at least four weeks and present most of the time.

#### **Domain B1- Behaviour:**

Loss of, or diminished, goal-directed behaviour as evidenced by at least one of the following:

- Initiation symptom: loss of self-initiated behaviour (for example: starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices).
- Responsiveness symptom: loss of environment-stimulated behaviour (for example: responding to conversation, participating in social activities).

**Domain B2 - Cognition:**

Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:

- Initiation symptom: loss of spontaneous ideas and curiosity for routine, and new events (i.e., challenging tasks, recent news, social opportunities, personal/family, and social affairs).
- Responsiveness symptom: loss of environment-stimulated ideas and curiosity for routine and new events (i.e., in the person's residence, neighbourhood or community).

**Domain B3–Emotion:**

Loss of, or diminished, emotion as evidenced by at least one of the following:

- Initiation symptom: loss of spontaneous emotion, observed or self-reported (for example, subjective feeling of weak or absent emotions, or observation by others of a blunted affect).
- Responsiveness symptom: loss of emotional responsiveness to positive or negative stimuli or events (for example, observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news).

- C. These symptoms (A - B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.
- D. The symptoms (A - B) are not exclusively explained or due to physical disabilities (e.g., blindness and loss of hearing), to motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance (e.g., drug of abuse, a medication).

**Unified Parkinson's Disease Rating Scale (UPDRS) <sup>5</sup>**

The UPDRS is the most widely used assessment scale in PD and consists of four sections. It includes: 1) Mentation, Behaviour, and Mood, 2) Activities of Daily Living, 3) Motor symptoms, and 4) Complications of Therapy. These are evaluated by interview and clinical observation. The items are scored on a five-point scale ranging from 0 to 4, with increasing scores indicating more severe symptoms.

### Hoehn and Yahr rating scales (H&Y) <sup>6</sup>

The H&Y scale is a commonly used system for describing how the symptoms of PD progress. The original scale included stages 1 through 5. Since then, stage 0 and stages 1.5 and 2.5 has been added. This modified scale allocates stages from 0 to 5 to indicate the relative level of disability.

- Stage 0: No signs of disease
- Stage 1: Unilateral symptoms only
- Stage 1.5: Unilateral and axial involvement
- Stage 2: Bilateral symptoms. No impairment of balance
- Stage 2.5: Mild bilateral disease with recovery on pull test
- Stage 3: Balance impairment  
Mild to moderate disease  
Physically independent
- Stage 4: Severe disability, but still able to walk or stand unassisted
- Stage 5: Needing a wheelchair or bedridden unless assisted

### Hamilton Depression Rating Scale (HAMD) <sup>7</sup>

The interviewer-rated HAMD is the most widely used and accepted measure for evaluating the severity of depression. Its use as a screening measure has been criticized and somatic items are heavily represented. Although it covers DSM-IV criteria incompletely, it has acceptable discriminant validity, high sensitivity, and high specificity. Multiple versions of the scale exist, of which the 17-item version is the most frequently used.

### Montgomery-Åsberg Depression Rating Scale (MADRS) <sup>8</sup>

The MADRS is an observer-rated scale. It covers all the DSM-IV criteria of a major depressive episode, with the exception of psychomotor retardation/agitation and reverse neurovegetative symptoms (hypersomnia and increased appetite). When compared to other observer-rated scales, such as the HAMD, the MADRS has relatively few somatic items. It was designed to measure change in severity of depressive symptoms, it is not usually used for screening purposes.

### **Neuropsychiatric Inventory (NPI)**<sup>9, 10</sup>

The NPI was developed as a structured interview conducted by the clinician to assess 10 forms of behavioural disorder that occur in patients with dementia, including delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behaviour. Subsequently a 12 item version was developed that also included sleep and appetite disturbances. All items consist of a screening question followed, in case of a positive answer, by additional questions estimating the frequency and severity of the symptom.

### **Apathy Evaluation Scale (AES)**<sup>11, 12</sup>

The AES is an 18-item, four-point Likert-type scale for the assessment of symptoms of apathy. Each question has four possible answers ranging from 1 to 4 (range 0–72), with higher scores indicating higher levels of apathy. The 18 items include four self-evaluation items that are scored exclusively on the patient's rating and one item requiring the rater to evaluate the patient's insight. There are patient-rated, clinician-rated, and informant-rated versions.

### **Lille Apathy Rating Scale (LARS)**<sup>13</sup>

The LARS is a recently developed scale that consists of 33 items divided into 9 domains. It is administered to the patient as a structured interview. The first three questions are scored on a five-point Likert scale, whereas the remaining items are answered as 'yes' or 'no'. The LARS total score ranges from –36 to +36 points, with positive scores indicating more severe apathy. The LARS was especially designed for patients with PD.

### **Mini Mental State Examination (MMSE)**<sup>14</sup>

The MMSE is a formalized mental status examination useful for identifying cognitively impaired patients. It is a simple and universally applied scale that can be easily and rapidly performed by a clinician. It exists of a number of short questions and tasks, aimed at memory function, orientation, language, praxis, and concentration. The MMSE is relatively insensitive to executive dysfunction.

**Cambridge Cognitive Examination (CAMCOG) <sup>15</sup>**

The CAMCOG is part of the Cambridge Examination for Mental Disorders of the Elderly. It evaluates a broad range of cognitive functions and can be divided into ten different subdimensions, each covering a specific cognitive domain: orientation, language (comprehension and expression), memory (recent, remote, and new learning), attention, praxis, abstract thinking, and perception. Total scores range between 0 (severe cognitive impairment) and 105 (no cognitive impairment). The CAMCOG is often used for the diagnosis and gradation of dementia and one of its major advantages is the ability to detect mild forms of cognitive impairment.

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## APPENDIX



## MOOD & MOTIVATION IN PARKINSON'S DISEASE



# SUMMARY

English

## MOOD & MOTIVATION IN PARKINSON'S DISEASE

This thesis is concerned with psychopathology in patients with Parkinson's disease (PD). PD is the most common movement disorder and the second most common neurodegenerative disorder after Alzheimer's disease. Psychopathological symptoms are common in PD and significantly contribute to disability, reduced quality of life, and caregiver distress. The first aim of this thesis is to identify patient subgroups based on motor and psychopathological symptoms. The second aim is to address some diagnostic issues of two very common psychopathological symptoms in PD: depression and apathy.

The main research questions of this thesis are:

- Can we establish subtypes of PD patients on the basis of motor and psychopathological symptoms?
- What is the prevalence of depression and apathy in PD patients?
- How do motor symptoms contribute to the diagnosis of depression in PD?
- Are the proposed diagnostic criteria for apathy valid?
- What are the neuroanatomical correlates of apathy in PD patients?

In Chapter 2, a systematic review of prevalence studies of depression in PD is described. The aim of this systematic review was to calculate average prevalences of depressive disorders taking into account the different settings and different diagnostic approaches of studies. A systematic literature search was carried out and a total of 104 articles were included and assessed for quality; 51 articles fulfilled the quality criteria. Multiple publications from the same database were not included in the meta-analysis. In the remaining 36 articles, the weighted prevalence of major depressive disorder was 17% of PD patients, that of minor depression 22% and dysthymia 13%. Clinically significant depressive symptoms, irrespective of the presence of a DSM defined depressive disorder, were present in 35%. In studies using a (semi-) structured interview to establish DSM criteria, the reported prevalence of major depressive disorder was 19%, while in studies using DSM criteria without a structured interview, the reported prevalence of major depressive disorder was 7%. Population studies report lower prevalence rates for both major depressive disorder and the clinically significant depressive symptoms than studies in other settings. This systematic review suggests that the average prevalence of major depressive disorder in PD is substantial, but lower than generally assumed.

In Chapter 3, a study to assess the influence of somatic symptoms of the Hamilton Depression Rating Scale (HAMD) and Montgomery-Åsberg Depression Rating Scale (MADRS) on the clinimetric performance of these scales in patients with PD is described. 224 patients underwent a protocolized mental state examination, consisting of the Structured Clinical Interview for DSM IV depressive disorder (SCID-D), as well as

the HAMD and MADRS. Sensitivity, specificity, positive, and negative predictive values for a range of cut-off scores were calculated for both rating scales and for modified versions of these scales in which all somatic items were eliminated. In addition, receiver operating characteristic curves were obtained for both the modified and unmodified scales. The results showed that elimination of the somatic items of depression from the HAMD and MADRS resulted in a reduced specificity of both the HAMD and the MADRS, and an increased sensitivity of the MADRS. We recommend the full version of the HAMD and MADRS if used for diagnostic purposes; for screening purposes, the abbreviated version without somatic items can be used. Additional advantages of using full rating scales, with somatic items included, are that these provide more information on the severity of depression and allow for easier comparison across studies.

In Chapter 4, a cluster analysis study is described to investigate the association between motor subtypes and psychopathology in PD. An exploratory and confirmatory cluster analysis of motor and psychopathological symptoms was performed with a randomized sample of 173 patients each, stemming from two research databases: one from Stavanger University Hospital and one from Maastricht University Hospital. These databases contained data of standardized assessments of patients with the Unified Parkinson's Disease Rating Scale, the Montgomery-Åsberg Depression Rating Scale, and the Mini Mental State Examination. The results showed that PD patients can be accurately and reliably classified into four different subtypes: rapid disease progression subtype, young-onset subtype, non-tremor-dominant subtype with psychopathology, and a tremor-dominant subtype. Cognitive deterioration, depressive and apathetic symptoms, and hallucinations all cluster within the non-tremor-dominant motor subtype, that is characterized by hypokinesia, rigidity, postural instability, and gait disorder.

In Chapter 5, a validation study of the proposed diagnostic criteria for apathy in PD is described. In a cross-sectional study, PD outpatients visiting a movement disorders clinic underwent a protocolized assessment of motor function, activities of daily living, cognition, and mood. In addition, the diagnostic criteria for apathy were administered as well as two apathy rating instruments: Lille Apathy Rating Scale (LARS) and the apathy section of the Neuropsychiatric Inventory (NPI). The results showed that 17.2% of the included patients were diagnosed as apathetic according to the criteria. Acceptability and internal consistency of the criteria was good, as was the concurrent validity with the LARS and apathy section of the NPI. Discriminant validity of the criteria with depression was moderate too good. All domains of criterion B (behaviour, cognition, emotion) contributed to the diagnosis of apathy, of which reduced goal-directed behaviour was most frequently observed. We concluded that the recently proposed diagnostic criteria for apathy are useful in clinical practice and in research with PD patients with and without cognitive impairment.

diagnostic criteria for apathy are useful in clinical practice and in research with PD patients with and without cognitive impairment.

In Chapter 6, a structural imaging study to determine the correlates of apathy in PD patients is described. Sixty PD patients underwent a neuropsychiatric and neuropsychological examination, and a 3 tesla magnetic resonance imaging scan was acquired. A voxel-based multiple regression analysis was used to calculate correlation between grey matter density and severity measures of apathy. The results showed that apathy correlates with decreased cognitive functioning and more depressive symptoms but not with more severe motor symptoms. High apathy scores were correlated with low grey matter density values in a number of cortical brain areas: the bilateral precentral gyrus, the bilateral inferior parietal gyrus, the bilateral inferior frontal gyrus, the bilateral insula, the right (posterior) cingulate gyrus and the right precuneus. We concluded that involvement of the cingulate gyrus and inferior frontal gyrus is in line with the results of earlier studies addressing apathy in patients with Alzheimer's disease and in patients with depressive disorder.

In Chapter 7, the results presented in this thesis are discussed. Methodological issues and clinical implications are addressed. Finally, recommendations for further research are given.

## MOOD & MOTIVATION IN PARKINSON'S DISEASE



# **SAMENVATTING**

Nederlands



## MOOD & MOTIVATION IN PARKINSON'S DISEASE

Het onderzoek beschreven in dit proefschrift richt zich op psychopathologische symptomen bij patiënten met de ziekte van Parkinson (ZvP). De ZvP is de meest voorkomende bewegingsstoornis en de op één na meest voorkomende neurodegeneratieve ziekte, op de ziekte van Alzheimer na. Psychopathologische symptomen zijn veel voorkomend bij de ZvP en leiden tot een verminderde kwaliteit van leven, een toegenomen belasting voor de partner/verzorgers en meer beperkingen in het dagelijks leven. Het eerste doel van het onderzoek beschreven in dit proefschrift is het identificeren van subgroepen van patiënten gebaseerd op zowel motorische als psychopathologische symptomen. Het tweede doel is het behandelen van enkele diagnostische vraagstukken omtrent twee veel voorkomende psychopathologische symptomen bij de ZvP: depressie en apathie.

De belangrijkste onderzoeksvragen kunnen als volgt worden geformuleerd:

- Kunnen we subgroepen van patiënten met de ZvP vaststellen op basis van motorische en psychopathologische symptomen?
- Wat is de prevalentie van depressie en apathie bij patiënten met de ZvP?
- Wat is de invloed van motorische symptomen bij het diagnosticeren van depressie bij de ZvP?
- Zijn de voorgestelde diagnostische criteria voor apathie bij de ZvP valide?
- Wat zijn de neuronanatomische correlaten van apathie bij patiënten met de ZvP?

In hoofdstuk 2 wordt een systematisch literatuuroverzicht van prevalentie studies van depressie bij de ZvP beschreven. Het doel van dit systematisch overzicht is om gewogen prevalenties van depressieve stoornissen bij de ZvP te berekenen, waarbij rekening wordt gehouden met verschillende settings en verschillende diagnostische benaderingen die gebruikt worden in de geïnccludeerde studies. In totaal werden 104 artikelen geïnccludeerd en beoordeeld op kwaliteit aan de hand van vastgestelde kwaliteitscriteria; 51 artikelen voldeden aan de kwaliteitscriteria. Publicaties gebaseerd op dezelfde onderzoekspopulatie werden vervolgens geëxcludeerd waardoor er 36 artikelen uiteindelijk werden meegenomen in de analyses. De gewogen prevalentie van een 'depressieve stoornis', een 'subklinische depressie' en een dysthyme stoornis waren respectievelijk 17%, 22% en 13%. Klinisch significante depressieve symptomen, ongeacht de aanwezigheid van een diagnose 'depressieve stoornis' volgens de DSM criteria, waren aanwezig in 35% van de parkinson patiënten. In studies die gebruik maakten van een (semi-) gestructureerd interview om een DSM diagnose vast te stellen, was de prevalentie van een depressieve stoornis 19%, terwijl in studies die geen gebruik maakten van een gestructureerd interview, de prevalentie van een depressieve stoornis 7% was. Bevolkingsstudies rapporteerden een lagere prevalentie voor zowel een depressieve stoornis als klinisch significante depressieve symptomen dan studies

gebaseerd op andere populaties. Dit systematisch overzicht laat zien dat de gewogen prevalentie van een depressieve stoornis bij de ZvP behoorlijk is, maar lager dan over het algemeen werd vermoed.

In hoofdstuk 3 wordt een onderzoek beschreven naar de invloed van somatische symptomen van de Hamilton Depression Rating Scale (HAMD) en de Montgomery-Åsberg Depression Rating Scale (MADRS) op de klinimetrische eigenschappen van deze schalen bij patiënten met de ZvP. In totaal ondergingen 224 patiënten een geprotocolleerd mentale status onderzoek, bestaande uit een gestructureerd klinisch interview om de DSM IV criteria voor een depressieve stoornis te kunnen vaststellen (SCID-D). Tevens werden de HAMD en de MADRS afgenomen. Sensitiviteit, specificiteit, positief en negatief voorspellende waarden werden berekend voor een reeks van afkappunten, voor zowel de gewone depressieschalen als voor een aangepaste versie van deze depressieschalen waarbij alle somatische items werden geëlimineerd. Ook werden 'receiver operating characteristic' curven berekend voor zowel de gewone als de aangepaste depressieschalen. De resultaten lieten zien dat eliminatie van de somatische items van de HAMD en MADRS, resulteerde in een afgenomen specificiteit van zowel de HAMD als de MADRS, en een toegenomen sensitiviteit van de MADRS. Onze aanbeveling is het gebruik van de originele versies van de HAMD en de MADRS, voor diagnostische doeleinden. Als screeningsinstrument kunnen de aangepaste versies, zonder somatische items, worden gebruikt. Bijkomende voordelen van het gebruik van de originele versies, met somatische items, zijn dat deze meer informatie geven over de ernst van de depressie en dat het vergelijken tussen verschillende studies makkelijker is.

In hoofdstuk 4 wordt een clusteranalyse beschreven met als doel het identificeren van subgroepen van patiënten met de ZvP op basis van motorische en psychopathologische symptomen. Een exploratieve en een confirmatieve clusteranalyse werd uitgevoerd op een gerandomiseerde steekproef van ieder 173 patiënten. Deze gegevens zijn afkomstig uit databases van twee verschillende onderzoeksgroepen: Stavanger University Hospital en Academisch Ziekenhuis Maastricht. Deze databases bevatten gegevens van gestandaardiseerde evaluaties van patiënten met de Unified Parkinson's Disease Rating Scale, de Montgomery-Åsberg Depression Rating Scale, en de Mini Mental State Examination. De resultaten toonden aan dat patiënten met de ZvP nauwkeurig en betrouwbaar kunnen worden ingedeeld in vier verschillende subtypes: een 'young-onset' subtype, een 'rapid disease progression' subtype, een 'tremor-dominant' subtype en een 'non-tremor-dominant' subtype met psychopathologische symptomen. Cognitieve achteruitgang, depressieve symptomen, apathie en hallucinaties clusteren allemaal binnen het niet-tremor-dominante subtype, dat wordt gekenmerkt door hypokinesie, rigiditeit, posturale instabiliteit en loopproblemen.

In hoofdstuk 5 wordt een validatiestudie van de voorgestelde diagnostische criteria voor apathie bij de ZvP beschreven. In een cross-sectionele studie, bezochten poliklinische patiënten met de ZvP een bewegingsstoornissen poli en ondergingen een geprotocolleerde beoordeling van de motorische functies, zelfredzaamheid (ADL functies), cognitie en stemming. Bovendien werden de diagnostische criteria voor apathie aan de hand van een interview beoordeeld en twee apathie beoordelingsschalen afgenomen; de Lille Apathy Rating Scale (LARS) en de Neuropsychiatric Inventory (NPI). De resultaten lieten zien dat 17,2% van de geïnccludeerde patiënten met de ZvP werden gediagnosticeerd als apathisch volgens de criteria. Aanvaardbaarheid en de interne consistentie van de criteria waren goed, net als de convergente validiteit met de LARS en het apathie gedeelte van de NPI. De discriminante validiteit van de criteria met depressie was matig tot goed. Alle domeinen van criterium B (gedrag, cognitie, emotie) droegen bij tot de diagnose van apathie, waarvan verminderd doelgericht gedrag het meest frequent werd gerapporteerd. We concludeerden dat de onlangs voorgestelde diagnostische criteria voor apathie nuttig zijn in de klinische praktijk en voor onderzoek met parkinson patiënten met en zonder cognitieve achteruitgang.

In hoofdstuk 6 wordt een structureel beeldvormingonderzoek naar de neurale correlaten van apathie bij patiënten met de ZvP beschreven. Zestig patiënten ondergingen een neuropsychiatrisch en neuropsychologisch onderzoek. Tevens werd een 3 tesla MRI-scan van het brein gemaakt. Vervolgens werd een voxel-based regressie analyse gebruikt om de relatie te onderzoeken tussen de ernst van de apathische symptomen en veranderingen van grijze stof volume. De resultaten lieten zien dat apathie correleerde met een verminderd cognitief functioneren en meer depressieve symptomen, maar niet met de ernst van de motorische symptomen. Hoge apathie scores correleerde met een verminderd grijze stof volume in een aantal corticale hersengebieden: de bilaterale precentrale gyrus, de bilaterale inferieur parietale gyrus, de bilaterale inferieur frontale gyrus, de bilaterale insula, de rechter (posterior) cingulate gyrus en de rechter precuneus. We concludeerden dat de betrokkenheid van de cingulate gyrus en inferieur frontale gyrus overeenkomt met de resultaten van eerdere onderzoeken naar de correlaten van apathie bij patiënten met de ziekte van Alzheimer en patiënten met een depressieve stoornis.

In hoofdstuk 7 worden de resultaten, beschreven in dit proefschrift, nogmaals kort besproken aan de hand van de gestelde onderzoeksdoelen. Daarnaast worden methodologische aspecten besproken en klinische implicaties van de bevindingen gegeven. Tenslotte worden er aanbevelingen voor toekomstig onderzoek gegeven.

## MOOD & MOTIVATION IN PARKINSON'S DISEASE



# **DANKWOORD**

J.S.A.M. Reijnders

## MOOD & MOTIVATION IN PARKINSON'S DISEASE

De afgelopen vier jaar zijn echt omgevlogen. Met enig ongeloof, maar zeker ook met trots, kan ik nu zeggen dat het proefschrift af is. In de afgelopen jaren heb ik met veel plezier onderzoek gedaan naar de psychopathologie bij de ziekte van Parkinson. Dit was natuurlijk niet mogelijk zonder de hulp van een heleboel mensen om me heen voor wie dit dankwoord geschreven is.

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DANKWOORD

## MOOD & MOTIVATION IN PARKINSON'S DISEASE



# **Curriculum Vitea**

J.S.A.M. Reijnders

## MOOD & MOTIVATION IN PARKINSON'S DISEASE

- 1980 Born on September 10<sup>th</sup> 1980, Heerlen, the Netherlands.
- 1993 – 1997 Higher General Secondary Education, Scholengemeenschap Sancta Maria, Kerkrade, the Netherlands.
- 1997 – 1998 Pre-university Education, Stercollege, Maastricht, the Netherlands.
- 1998 – 1999 Propaedeutics Economy, Maastricht University, Maastricht, the Netherlands.
- 1999 – 2006 Master in Psychology, Maastricht University, Maastricht, the Netherlands.  
Graduate direction: Neuropsychology and Cognitive Ergonomics.  
Title: "The role of Serotonin in Parkinson's disease".
- 2001 – 2005 Student-tutor at the Department of Psychology, Maastricht University, Maastricht, the Netherlands.
- 2005 Research-assistant at the Department of Neurology of the Bakken Research Centre Maastricht (Medtronic), the Netherlands.  
Project: "Evaluation of the effectiveness of neurostimulation in Parkinson's disease".
- 2005 – 2006 Clinical traineeship at the Department of Neuropsychiatry of the Psycho-medical Institute (PMS) Vijverdal (Mondriaan Zorggroep), Maastricht, the Netherlands.
- 2006 – 2007 Research-associate at the Department of Psychiatry and Neuropsychology, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands.
- 2007 – 2010 PhD-student at the Department of Psychiatry and Neuropsychology, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands.  
Project: "Apathy in patients with Parkinson's disease, a structural brain imaging study using voxel based morphometry".
- 2010 – Present Post-doctoral researcher at the Department of Psychiatry and Neuropsychology, Maastricht University Medical Centre, Maastricht, the Netherlands.





## **Publications**

J.S.A.M. Reijnders



## MOOD & MOTIVATION IN PARKINSON'S DISEASE

- Reijnders JSAM, Ehrt U, Weber WEJ, Aarsland D, Leentjens AFG. A systematic review of prevalence studies of depression in Parkinson's disease. *Movement Disorders* 2008;23:183-189 (Chapter 2).
- Reijnders JSAM, Ehrt U, Lousberg R, Aarsland D, Leentjens AFG. The association between motor subtypes and psychopathology in Parkinson's disease. *Parkinsonism & Related Disorders* 2009;15:379-382 (Chapter 4).
- Reijnders JSAM, Lousberg R, Leentjens AFG. Assessment of depression in Parkinson's disease: the contribution of somatic symptoms to the clinimetric performance of the Hamilton and Montgomery-Åsberg rating scales. *Journal of Psychosomatic Research* 2010;68:561-565 (Chapter 3).
- Reijnders JSAM, Scholtissen B, Weber WEJ, Aalten P, Verhey FRJ, Leentjens AFG. Neuroanatomical correlates of apathy in Parkinson's disease: a magnetic resonance imaging study using voxel-based morphometry. *Movement Disorders* 2010 (online ahead of print) (Chapter 6).
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- Reijnders JSAM, Leentjens AFG. Diagnostiek en beoordeling van psychopathologie bij de ziekte van Parkinson. Accepted for publication in *Tijdschrift voor Psychiatrie*.
- Reijnders JSAM, Schiphof F, Leentjens AFG. The validity of the Mini Mental State Examination in the detection of Parkinson's disease Dementia (in preparation).